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RELATIONSHIP BETWEEN RHEUMATIC AND SUBACUTE BACTERIAL ENDOCARDITIS

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It is well known that a heart once damaged by rheumatic disease is more liable to subsequent infection, especially with nonhemolytic streptococci. In a review of 330 cases of subacute bacterial endocarditis, Blumer [1] found that 168, or 50 per cent, of the patients had a definite history of rheumatism (140), chorea (10) and tonsillitis (18). In 20 cases of streptococcus viridans endocarditis that were analyzed by Thayer [2a] and that came to necropsy, 65 per cent of the patients had a history of rheumatism or chorea.[2b] In a survey of 115 cases of subacute bacterial endocarditis collected from the records of the Presbyterian Hospital (New York), Lamb [3] noted 94 patients (82 per cent) who were known to have had cardiac damage, and of these, 69, or 60 per cent of the entire series, gave a history of rheumatism. In a group of 111 cases of subacute bacterial endocarditis studied by Fulton and Levine [4] 50 of the patients had a history of previous rheumatism. The most recent studies of rheumatic fever (White and Jones [5]) indicated that 4.1 per cent of the patients (39 of 956) later succumbed to subacute endocarditis.

These citations will suffice to indicate the general frequency of the association of the two diseases.

While there is thus abundant statistical evidence for a relation between rheumatic fever and subacute bacterial endocarditis, various conceptions may be held as to the nature of this relationship: (1) The lesions of rheumatic and bacterial endocarditis are reactions of different

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1. Blumer, G.: Subacute Bacterial Endocarditis, Medicine **2**:105, 1923.

2. (*a*) Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Rep. **22**:1, 1926; (*b*) p. 84; (*c*) p. 15.

3. Lamb, A. R.: Personal communication to the authors.

4. Fulton, M. M., and Levine, S. A.: Subacute Bacterial Endocarditis with Special Reference to the Valvular Lesions and Previous History, Am. J. M. Sc. **183**:60, 1932.

5. White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, Am. Heart J. **3**:302 (Feb.) 1928.

intensity to the same infection, or (2) subacute bacterial endocarditis is a secondary infection, superimposed on (*a*) old or healed rheumatic valvular lesions or (*b*) recent or active rheumatic vegetations. It is this last theory, so little stressed in the literature, that we wish to substantiate with evidence gathered from a close study of our material obtained at necropsy. It may be well, however, to cite in detail the views of recent workers in support of each of these possibilities.

The view that both processes represent reactions of different intensity to the same causative agent (streptococci) is maintained by Clawson and Bell,[6a] who have been impressed with the frequency with which the two types of lesions are found in the same heart. In their words,

> From a study of a large number of cases, we get the impression that these two forms of endocarditis represent mild and severe degrees of the same infection.[6b] . . . Histological studies of the valve leaflets indicated also that the two forms of endocarditis differ only in the intensity of the inflammatory process.[6c]

In their summary, they stated again:

> In both types there is a proliferative inflammation in the valve, but the thrombus over the infected area is larger and softer in the subacute lesion. The streptococci, generally the viridans strain, seem to be responsible for both rheumatic and subacute bacterial endocarditis.

Clawson, Bell and Hartzell[7a] expressed the same point of view when they stated, in reference to the commonly observed transition between the two types of lesions:

> Unless the improbable assumption is made that three-fourths of the subacute bacterial cases have a simultaneous rheumatic infection, it must be granted that rheumatic and bacterial endocarditis are caused by the same organism.[7b]

In a recent review of the Aschoff nodule, Clawson[8] again emphasized the frequency with which proliferative inflammation of the valves, like that found in acute rheumatic endocarditis, occurs in cases of subacute bacterial infection. He again drew the conclusion that this association, as well as the frequently found Aschoff nodules in the myocardium (45 per cent of 60 cases), indicated a common etiology.

Jaffé[9a] also described noninfected verrucae and subendothelial cell palisades occurring side by side with vegetations containing bacteria and composed of thrombotic deposits, necrotic tissue, giant cells and wandering cells of various types. Without committing himself definitely on

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6. (*a*) Clawson, B. J., and Bell, E. T.: A Comparison of Acute Rheumatic and Subacute Bacterial Endocarditis, Arch. Int. Med. **37**:66 (Jan.) 1926; (*b*) p. 67; (*c*) p. 79.

7. (*a*) Clawson, B. J.; Bell, E. T., and Hartzell, T. B.: Valvular Disease of the Heart with Special Reference to the Pathogenesis of Old Valvular Defects, Am. J. Path. **2**:193 (May) 1926; (*b*) p. 230.

8. Clawson, B. J.: The Aschoff Nodule, Arch. Path. **8**:664 (Oct.) 1929.

9. Jaffé, R. H.: (*a*) Zur Histologie der Herzklappenveränderungen bei der Endocarditis lenta, Virchows Arch. f. path. Anat. **287**:379, 1932; (*b*) p. 391.

the question of the etiology, he said that these observations can be interpreted in the sense of a causal relationship between endocarditis lenta and rheumatic endocarditis. ("Können auch die hiermitgeteilten Befunde im Sinne einer ursächlichen Verwandschaft zwischen lenta und rheumatischer Endokarditis gewertet werden.[9b])

These quotations will serve to illustrate the point of view of the investigators who, struck by the frequency of this association, deduce a common streptococcic origin.

The second theory, that the bacterial vegetations are engrafted on valves *previously* damaged by rheumatic disease is the one usually given. Thus Coombs[10] stated that "these forms of valvular infection (i. e., endocarditis lenta) often arise on a basis of old valvular sclerosis of rheumatic infection." Ribbert[11] declared:

> Mit besondere Vorliebe entwickelt sich die maligne Endocarditis auf schon pathologisch veränderten Klappen. Daher sind ihre Prädilektionsstellen arteriosklerotische Klappenläsionen oder alte rheumatische Klappenverdickungen. (Malignant endocarditis develops especially on pathologically altered valves. The sites of predilection are therefore arteriosclerotic lesions of the valves or old rheumatic thickenings.)

Thayer stated:

> It is difficult to escape the conclusion that the frequent involvement of the wall of the left auricle in subacute streptococcus endocarditis is dependent on the same predisposing causes as in the case of the valves themselves—namely, the existence of scarred and sclerotic areas, the result of preceding rheumatic disease; these areas seem to be especially vulnerable.[2e]

Swift stated:

> The bacterial endocarditis is practically always secondary; in other words, the bacteria are implanted in or on an abnormal valve, and in the majority of instances, the valve has been the seat of an old rheumatic endocarditis.[12]

MacCallum[13] said:

> It seems probable that many of the cases of bacterial endocarditis arise because the valves have been injured by rheumatic infection. . . .

And again,

> We have observed in rheumatism a peculiar patch of thickening of the wall of the left auricle . . . which ends in the formation of a puckered scar there, and in the cases of streptococcus viridans endocarditis this same place forms the site of vegetations in very many cases.

10. Coombs, C. F.: Rheumatic Heart Disease, New York, William Wood & Company, 1924, p. 31.

11. Ribbert, H.: Die Erkrankungen des Endokards, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 223.

12. Swift, H.: The Heart in Infection, Am. Heart J. **3**:12, 1928.

13. MacCallum, W. G.: Textbook of Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1932, pp. 237 and 504.

In discussing the relation of rheumatism to subacute bacterial endocarditis, Boyd [14] said, "We know that subacute endocarditis very frequently develops on top of a previous rheumatic lesion."

The third possibility, that the bacteria are implanted on *recent active* rheumatic lesions, has received little consideration. This is the more surprising in that in a number of recent studies of the disease investigators have noted the frequency of the occurrence of active rheumatic endocarditis and subacute bacterial endocarditis in the same heart. We have already referred to the extensive observations of Clawson and Bell,[6a] Clawson, Bell and Hartzell [7a] and Clawson [8] and shall have occasion again to discuss the conclusions which they derived. Libman [15] recorded a case of this sort, in which both types of endocarditis existed. Leary [16] cited an interesting case in a boy, aged 6 years, who was run over and instantly killed. Autopsy revealed endocarditis of the mitral valve, which was found on histologic examination to be rheumatic, and his case was used to illustrate the characteristic cellular reaction of the rheumatic valvulitis. On the surface of the vegetation, however, were large colonies of gram-positive diplococci, which on culture proved to be Streptococcus viridans.

In a series of 10 cases of subacute bacterial endocarditis in children, Saphir and Wile [17a] found Aschoff bodies in every case. In discussing the relationship between the rheumatic infection and subacute bacterial endocarditis, these investigators, though accepting the specificity of the Aschoff body, were led to conclude that the "coincidental occurrence of these two conditions, though not definitely excluded, seems unlikely." [17b] We regard it more logical to draw the opposite conclusion.

In his discussion of their paper, Libman [18] said that he had "long ago noted combinations of active subacute bacterial endocarditis and recent rheumatic infections."

Although the coincidence of active rheumatic lesions with subacute bacterial endocarditis has thus attracted the attention of several observers, we have not seen expressed the view that active rheumatic vegetations are, in persons who have had rheumatism, a necessary and practically constant prerequisite for the implantation of the bacteria.

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14. Boyd, W.: Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1931, p. 55.

15. Libman, E.: Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813 (March 24) 1923.

16. Leary, T.: Early Lesions of Rheumatic Endocarditis, Arch. Path. **13**:1 (Jan.) 1932.

17. (*a*) Saphir, O., and Wile, S. A.: Rheumatic Manifestations in Subacute Bacterial Endocarditis in Children, Am. Heart J. **9**:29, 1933; (*b*) p. 43.

18. Libman, E.: Am. Heart J. **9**:110, 1933.

				Rheumatic Lesions													
				Gross				Histologic									
						Endocardial		Acute					Subacute Bacterial Endocarditis				
Case	Age	Sex	History of Rheumatism	Adherent Pericardium	Myocardial Scars	Acute	Chronic	T	M	A	LA	Aschoff Bodies	T	M	A	LA	Comment
1	47	F	5 years ago	..	..	T, M	LA	+	+	..	..	+	..	+	..	..	
2	30	F	6 years ago	..	+	..	..	..	+	..	..	..	..	+	..	+	
3	60	M	?	+	..	M	..	..	+	..	..	..	..	+	+	..	Perivascular myocardial scars
4	43	F	Chorea 34 years ago	..	..	..	M	..	..	+	..	+	..	+	..	..	
5	11	F	3 years ago	+	..	M	..	..	+	..	..	..	..	+	..	+	Myocardial scars; rheumatic aortitis
6	44	M	0	..	..	T	..	..	+	+	..	..	..	+	+	..	Perivascular myocardial scars
7	42	M	0	..	..	..	M	..	+	..	..	+	..	+	+	..	
8	33	F	14 and 15 yrs. ago	..	+	..	M, A	..	+	..	..	+	..	+	+	..	Perivascular myocardial scars
9	9	F	4 years ago	+	..	T, M, A	LA	+	+	+	..	+	..	+	..	+	
10	37	M	6 mos. ago	..	+	M	M	..	+	..	..	+	..	+	..	+	
11	26	M	11 years ago	+	+	M	A, LA	..	+	..	..	+	..	+	+	+	
12	22	F	Past few years	+	+	T	M, A	+	..	..	+	+	..	+	+	+	Rheumatic aortitis
13	58	M	40 years ago	..	..	T	M	..	+	..	..	+ (M)	..	+	..	..	
14	15	F	5 years ago	+	+	T, M	M	+	+	..	+	..	..	+	+	+	Perivascular myocardial scars
15	24	F	12 years ago	..	+	..	M	..	+	..	..	..	..	+	..	+	
16	23	M	17, 13 and 3 years ago	..	..	..	M, LA	..	+	..	..	..	..	+	..	+	Perivascular myocardial scars
17	35	M	22 years ago	..	..	A	M, A	..	..	+	..	..	..	+	+	..	
18	42	M	25 years ago; chorea 38 years ago	..	..	M, A	M	..	+	+	..	..	..	+	+	..	Perivascular myocardial scars; rheumatic pulmonary arteritis
19	56	F	41 years ago	..	..	..	T, M, A	..	+	..	..	+ (M)	..	+	+	..	Perivascular myocardial scars
20	40	F	0	..	..	M	LA	..	+	..	..	+	..	+	+	..	
21	45	M	0	..	..	..	A	..	+	..	..	..	..	+	..	..	
22	25	M	12 years ago	..	..	M, A	LA	..	+	+	..	..	..	+	..	..	Perivascular myocardial scars; rheumatic arteritis of the prostate and intestine
23	28	F	? in childhood	+	+	T, M, A	..	+	+	+	..	..	+	+	+	+	Perivascular myocardial scars
24	41	F	1 year ago	..	..	..	M	..	+	..	..	..	..	+	+	+	Perivascular myocardial scars
25	13	F	Chorea 6 years ago	..	..	M, LA	..	..	+	..	+	+	..	+	..	+	
26	44	F	38 years ago	..	..	..	M, LA	..	+	..	..	..	..	+	..	..	Perivascular myocardial scars

* T indicates the tricuspid valve; M, the mitral valve; A, the aortic valve, and LA, the left auricle.

Our studies have driven us to this conclusion. The evidence for it may be summarized as follows:

1. Vegetations histologically identical with those in rheumatic endocarditis and not containing bacteria are found (*a*) on the same valve as the bacterial vegetations, (*b*) on other valves on which there are no vegetations containing bacteria and (*c*) on the auricular wall.

2. Aschoff bodies in the myocardium that are taken to indicate active rheumatic disease are found in practically the same proportion of cases of subacute bacterial endocarditis as of uncomplicated rheumatic cardiac disease.

3. Types of bacterial endocarditis other than that due to nonhemolytic streptococci may be engrafted on active rheumatic vegetations. This is a cogent argument against the view that the two types of lesions are a response of different intensity to the same infective agent, unless we dispense with current views as to the histologic specificity of the rheumatic reaction.

Our observations on a series of 26 consecutive cases of subacute bacterial endocarditis are summarized in the accompanying table. In 15 of the cases, the pathologist, in his objective description of the gross valvular lesions, noted the occurrence of small, firm verrucae, which were distinct from the larger, more friable thrombotic vegetations. In sections, in each of the 26 cases there were found bacteria-free vegetations having the histologic appearance of active rheumatic verrucae. In 24 of the 26 cases, the vegetations were situated on the same valves as the bacterial vegetations. In 6 cases, they were present on other valves, namely, on the aortic valve (three times) and on the tricuspid valve (four times). In many instances, vegetations that were otherwise indistinguishable from rheumatic verrucae contained bacterial colonies in their superficial portion (figs. 1 and 2). An unbroken transition could be traced between the bacteria-free rheumatic verrucae which were histologically rheumatic but contained bacteria and the larger thrombotic vegetations in which the presence of the bacteria had elicited a more or less violent cellular reaction and in which there was more or less destruction of the substance of the valve. In this we are able fully to confirm the observations of Clawson and Bell,[6b] although our interpretation is different.

In 12 of the 26 cases (46 per cent), characteristic Aschoff bodies were found in the myocardium or at the base of the mitral valve.

The frequency of the finding of Aschoff bodies in uncomplicated rheumatic carditis is variously given. In his review, published in 1925, Sacks[19] cited an incidence, as given by different authors, ranging from

19. Sacks, B.: The Pathology of Rheumatic Fever: A Critical Review, Am. Heart J. **1**:750, 1926.

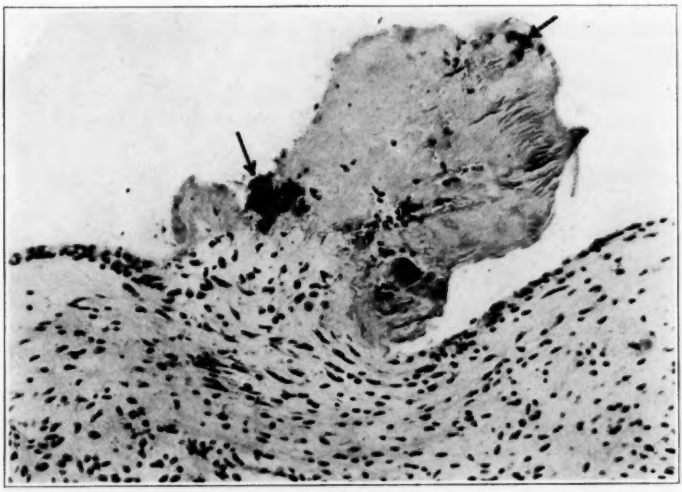

Fig. 1.—Rheumatic verruca of the mitral valve, showing the characteristic histologic conditions, but having colonies of bacteria (indicated by arrows). Note the absence of a cellular response.

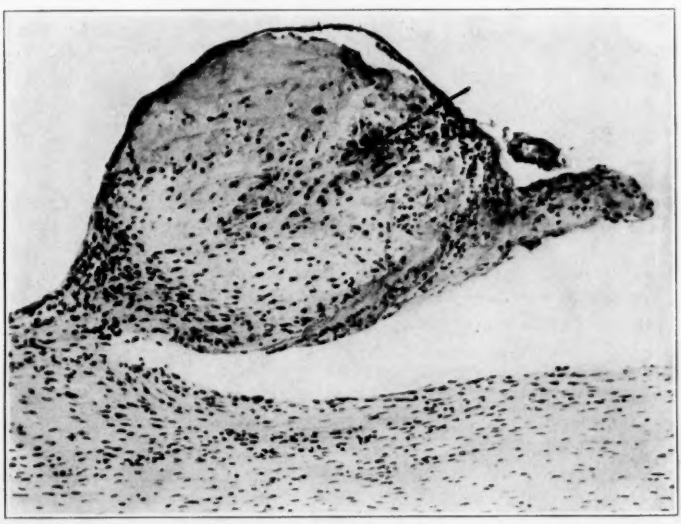

Fig. 2.—Healing rheumatic verruca containing a small colony of bacteria (arrow) with an early cellular response.

32.1 to 87.5 per cent. In 109 cases collected from our records of four years ago, Aschoff nodules were found in 46, or 42 per cent.

The incidence is therefore practically the same in our uncomplicated cases and in those with bacterial vegetations; it agrees with curious exactness with the 45 per cent incidence reported by Clawson [8] in his series of 60 cases of bacterial endocarditis.

Finally, one may cite cases in which active rheumatic lesions of the valves or myocardium existed with bacterial infections of the heart valves with micro-organisms other than Streptococcus viridans.

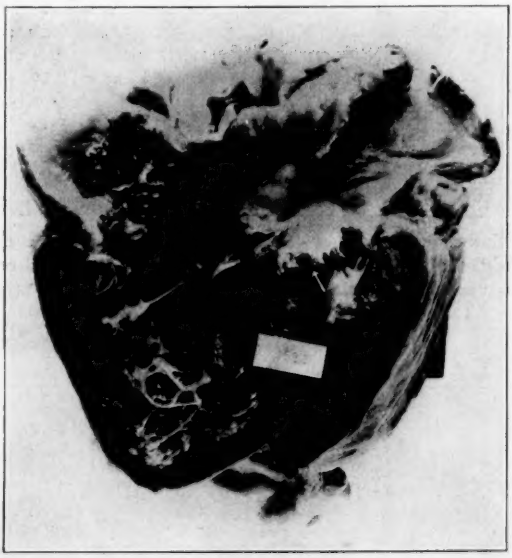

Fig. 3 (case 1).—Rheumatic and subacute bacterial endocarditis. Rheumatic verrucae on a nonaortic leaflet of the mitral valve.

The following cases will serve to illustrate the coincidence of active rheumatic carditis with subacute bacterial endocarditis.

REPORT OF CASES

CASE 1.—A girl, aged 11 years, had had two attacks of rheumatic fever, the first at the age of 10 and the second three and one-half months before her admission to the hospital. Following the second attack of arthritis, precordial pain, palpitation, dyspnea and weakness developed. On examination, the heart was found to be enlarged; precordial pulsation was marked; there were apical systolic and diastolic thrills, a loud, blowing systolic apical murmur and a short, rumbling diastolic murmur. Blood culture at this time yielded no growth.

A year later, the patient was readmitted because of abdominal pain, nausea, vomiting and tenderness in the little finger. The temperature was 104 F. Only

a loud systolic murmur could be detected. The liver was enlarged and tender. Tenderness was felt over the sternum and toe. There were red blood cells in the urine. The nonhemolytic streptococcus was found on blood culture. While the patient was in the hospital, hemiplegia and other embolic phenomena developed. Death occurred six months after the diagnosis of subacute bacterial endocarditis had been established.

Fig. 4 (case 1).—Subacute bacterial endocarditis of the mitral valve.

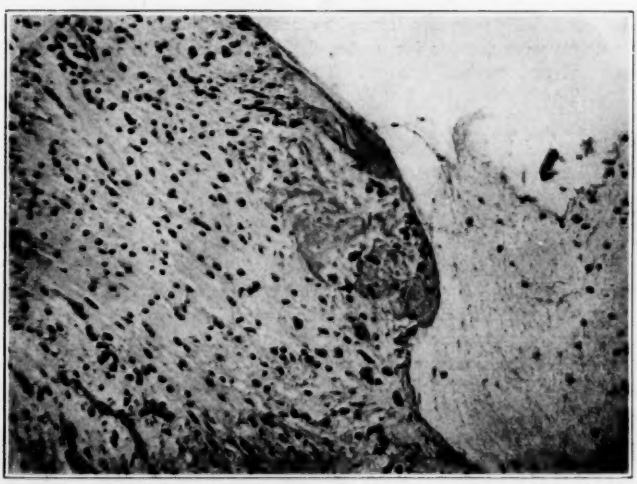

Fig. 5 (case 1).—Healing rheumatic verruca of the mitral valve.

The heart was enlarged and the pericardium adherent at the apex and over the great vessels, and there was 100 cc. of serofibrinous fluid in the remains of the pericardial cavity. The tricuspid and pulmonic valves were normal. On the mitral valve were large, friable, yellow-gray vegetations, which extended down on the chorda tendinae for a short distance and were continued across the auricular surface of the valve to the wall of the auricle. On the posterior half of the nonaortic leaflet were a few tiny, firm gray verrucous nodules with smooth surfaces (fig. 3). The aortic valves were normal.

In sections of the mitral valve, many of the excrescences had the usual appearance of bacterial vegetations; there were large colonies of gram-positive cocci on the surface, polymorphonuclears and large mononuclear cells filled with engulfed bacteria (fig. 4). There were also irregular clumps of calcium. Sections through the verrucae described earlier showed a different structure. There were no bacteria to be seen; the vegetation was composed of hyaline material partly covered with endothelium, with fibroblasts growing into the base (fig. 5). In the myocardium there were loose vascular scars and occasional compact avascular scars not sharply limited to the perivascular tissue. No Aschoff bodies were found in seven blocks.

This case thus illustrates the simultaneous occurrence of rheumatic and subacute bacterial vegetations on the mitral valve.

CASE 2.—A stenographer, aged 22, who had had poliomyelitis in infancy, scarlet fever at 9 years and influenza at 13, noted occasional pains in the joints without fever during the four years previous to admission. Although she had no cardiac symptoms, she was told two years before entrance that she had "heart disease."

The onset of the present illness, two months before entrance, was marked by fatigue, loss of appetite and irritability. For two weeks there was edema of the ankles, and tenderness of the finger-tips was noted on several occasions.

Examination showed hemorrhage into the fundus of the right eye, a slightly enlarged heart with murmurs, secondary anemia and continued irregular fever. Blood cultures were positive for nonhemolytic streptococci. Symptoms pointed to splenic, renal and cerebral infarcts. The diagnosis of subacute bacterial endocarditis was established. Death took place about six months after the onset of the symptoms.

The heart weighed 420 Gm. There were no pericardial adhesions. The tricuspid leaflets were narrowed and thickened. On the infundibular leaflet was a narrow, yellowish-gray ridge, 7 mm. in length, and somewhat granular; on the septal leaflet there was a translucent yellowish line, from 2 to 3 mm. in length, and slightly elevated. On both leaflets of the mitral valve were large, friable, yellowish-gray or reddish vegetations, extended on the chordae and upward on the auricle. The auricular endocardium above the nonaortic leaflet was roughened by numerous small, opaque vegetations between which the endocardium was thick and wrinkled. The aortic cusps had large, friable vegetations extending down onto the septal endocardium. There was a mycotic aneurysm in the sinus of Valsalva behind the left posterior leaflet; when the cusps were not covered by the vegetations, they were thickened, and the edges were rolled and nodular.

Microscopically, the vegetations on the tricuspid valve were composed of somewhat hyaline material into which vertically directed fibroblasts were growing. There were no polymorphonuclears and no bacteria. The substance of the valve was thickened and scarred (fig. 6).

The auricular endocardial lesions were also for the most part characteristically rheumatic, but in some places clumps of bacteria were present, and here there was intense polymorphonuclear reaction as well as many mononuclear cells. The mitral and aortic vegetations contained bacterial colonies and presented the usual picture

Fig. 6 (case 2).—Rheumatic endocarditis of the tricuspid valve.

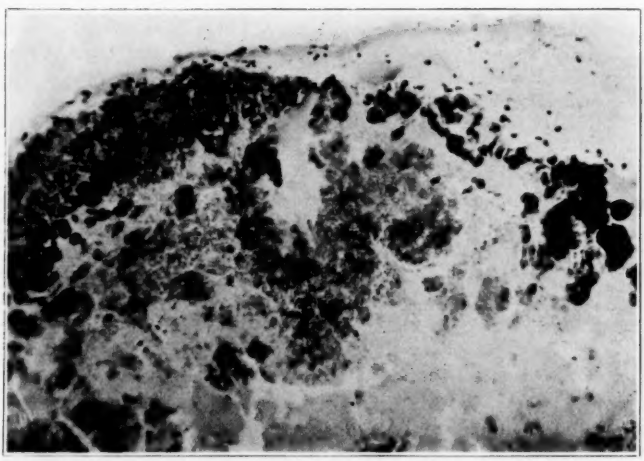

Fig. 7 (case 2).—Subacute bacterial endocarditis of the mitral valve.

seen in subacute bacterial lesions of these valves (fig. 7). In the myocardium were numerous Aschoff nodules.

In this case, in which there was a definite history of pains in the joints, characteristic old lesions and recent rheumatic lesions were found at autopsy on the tricuspid valve and the left auricle and in the myo-

cardium. The rheumatic changes on the aortic and mitral valves were obscured by the inflammatory reaction provoked by the streptococci.

That bacteria other than the streptococcus may be implanted on active rheumatic valvulitis is shown by the following case:

CASE 3.—A boy, aged 14, at 5 years of age was discovered to have heart trouble. For several years there had been occasional mild pains in the knees and hips. Two weeks before entrance, an injury to the fingers of the left hand, with resulting infection, occurred. Six days before entrance the patient suddenly became feverish, and several days later he had pains in the knees, hip, elbows and shoulder. The heart was greatly enlarged, with a double murmur at the mitral area. Hemolytic Staphylococcus aureus was obtained on blood culture and from the infected finger. The patient died after a profound sepsis which lasted eight days.

The heart weighed 380 Gm. The tricuspid and pulmonic valves were normal. The mitral valve was uniformly thickened, as well as the chordae tendineae. There was a bulky, thrombotic vegetation on the auricular surface of the nonaortic leaflet, which extended upward on the thickened auricular endocardium. The aortic cusps were also the seat of fresh thrombotic vegetations. There were miliary abscesses in the myocardium. Histologic study clearly showed a combination of old and recent rheumatic lesions with those attributable to the superimposed staphylococcic infection. On the mitral valve were areas free from bacteria, in which the subendocardial cells showed a characteristic palisading. The colonies of cocci were embedded in a compact pink-staining matrix that was being invaded by fibroblasts, and although there were many leukocytes in places, one had the impression that the vegetation was primarily rheumatic. Furthermore, groups of large basophilic cells resembling Aschoff bodies were found at the base of the vegetation. The myocardium contained fairly numerous typical Aschoff bodies in addition to old scars and staphylococcic abscesses.

In this case we believe that the two diseases coexisted; in other words, that the patient was suffering from active rheumatic carditis when the heart became infected with Staphylococcus aureus.

Further evidence that the two types of lesions are etiologically independent is thus afforded by case 3, in which hemolytic staphylococci were superimposed on rheumatic lesions.

COMMENT

It seems to us that the most obvious deduction from these observations is that bacteria are implanted superficially in the hyaline or granular material of which the rheumatic vegetation is composed, in other words, on an *active, unhealed* rheumatic lesion. It might be argued that bacteria-free vegetations on the same valve but at a distance from the main mass of the organisms are evoked by a diffusible toxin. But this assumption would not hold for cases in which bacteria-free rheumatic verrucae were situated on the tricuspid valve.

The presence of Aschoff bodies may be taken as further evidence of the activity of the rheumatic process in these cases. Our studies thus lead to the conclusion that it is not the old, scarred valve that is

predisposed to subsequent infection with bacteria but the valve or auricular wall which bears on its surface the fresh, unhealed verruca or plaque.

The fact that in many of our cases a long interval (in one instance, forty-one years) elapsed before the patient evinced rheumatic arthritis is no argument against this conception. It is now well established that rheumatic carditis may exist in a subclinical form for many years or without any history of a pathologic condition of the joint.

It is not maintained that all cases of bacterial infection of the valves are the result of implantation on unhealed rheumatic lesions. Nor do we wish to deny the possibility that infection of the valve in cases of general sepsis may occur through the blood vessels of the valves. We have in our records several cases in which an acute interstitial valvulitis was unaccompanied by vegetations, indicating that the infection had reached the substance of the valve through the coronary circulation.

CONCLUSIONS

Infection of the cardiac valves with nonhemolytic streptococci in rheumatic patients is due to the implantation of the bacteria on unhealed rheumatic vegetations. The continued activity of the rheumatic disease in cases of subacute bacterial endocarditis is attested by the invariable occurrence on the valves of rheumatic verrucae which do not contain bacteria and by Aschoff bodies in the myocardium in the same percentage of cases as in uncomplicated rheumatic carditis. Staphylococcus aureus may also be implanted on unhealed rheumatic vegetations.

Dr. Walter W. Palmer and Dr. Allen O. Whipple permitted us to transcribe the clinical records.

1. Bach -

STERNAL MARROW ASPIRATED DURING LIFE

CYTOLOGY IN HEALTH AND IN DISEASE

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Although the importance of studies of the bone marrow in hematologic disorders is well known, few examinations of the bone marrow have been made during life. Simultaneous examinations of the peripheral blood and the bone marrow have been made feasible by Arinkin's [1] simple method of obtaining bone marrow by sternal puncture. Using a similar technic, we have studied the marrow of twenty-eight healthy men and twenty-six patients.

Ghedini [2] was apparently the first to describe a technic for taking a specimen of bone marrow for biopsy. His method of trephining the tibia was little used. Seyfarth [3] also used a method of trephining, but suggested that the sternum was more suitable for routine studies than the tibia. Peabody [4] studied the bone marrow in pernicious anemia, using Ghedini's technic for the removal of marrow. His work has done much to establish the procedure as a diagnostic aid and as a reliable method of studying the function of bone marrow.

Arinkin [1] introduced a simple technic for obtaining bone marrow from the manubrium sterni by aspiration through a spinal puncture needle. Since then investigations by Arinkin [5], and by other European

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1. Arinkin, M. I.: Methodology of Examining Bone Marrow in Live Patients with Hematopoietic Diseases, Vestnik khir. **10**:57, 1927.

2. Ghedini, G.: Per la patogenesi e per la diagnosi delle malattie del sangue e degli organi emopoietici, punctura esplorativa del midollo osseo, Clin. med. ital. **47**:724, 1908; Neue Beiträge zur Diagnostik der Krankheiten der hämatopoetischen Organe mittels Probepunktion des Knochenmarks, Wien. klin. Wchnschr. **23**:1840, 1910; Die Technik der Knochenmarkspunktion, ibid. **24**:284, 1911; cited by Peabody.[4]

3. Seyfarth, C.: Die Sternumtrepanation, eine einfache Methode zur diagnostischen Entnahme von Knochenmark bei Lebenden, Deutsche med. Wchnschr. **49**:180 (Feb. 9) 1923.

4. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, Am. J. Path. **3**:179 (May) 1927.

5. Arinkin, M. I.: (*a*) Morphologic Changes in Composition of Bone Marrow Obtained from the Thoracic Cavity by Puncture in Cases of Pernicious Anemia During Remissions, Klin. med. **7**:135, 1929; (*b*) Die intravitale Untersuchungsmethodik des Knochenmarks, Folia haemat. **38**:233 (June) 1929.

workers [6] have shown that this is a practical and useful clinical procedure. The excellent description and analysis of this technic by Tuschinsky and Kotlarenko [6d] is worthy of special mention. The only American publication is a short report by Holmes and Broun.[7] Few studies on normal persons have been included in the published reports. Broun's [8] excellent preparations, seen while visiting his laboratory (E. E. O.), and the lack of normal standards led to our selection of this problem for study.

TECHNIC OF STERNAL PUNCTURE

The technic of sternal puncture that we found to be most satisfactory is as follows: With the patient lying on his back, with his chest elevated by a pillow beneath his shoulders, the region of the sternomanubrial junction is prepared with iodine and alcohol. Using aseptic technic, the sternomanubrial junction is located as a distinct ridge opposite the sternal cartilages of the second ribs, and the skin, the subcutaneous tissues and the periosteum of the region are infiltrated with procaine hydrochloride. Using an 18 gage spinal puncture needle, from 3 to 4 cm. in length, the sternomanubrial junction is entered in the midline at an angle of about 60 degrees to the surface of the chest. Then the needle is depressed to an angle of about 30 degrees and is forced into the marrow cavity of the body of the sternum, care being taken not to exceed a depth of 1.5 cm. If much resistance is encountered, the needle is rotated while pressure is maintained to facilitate penetration. The stylet is then removed, and, using a 2 cc. Luer syringe, 1 or 2 cc. of marrow is aspirated. If no marrow appears after strong aspiration, the stylet is replaced, the needle is inserted a little deeper and aspiration is done. We then remove the syringe from the needle and transfer the aspirated material, which looks like blood, into a 4 by ½ inch (10.16 by 1.27 cm.) test tube containing from 2 to 4 mg. of powdered potassium oxalate shaking well to insure mixing. The stylet is then replaced, the needle is withdrawn and the puncture wound is sealed with collodion.

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6. (*a*) Pokrovsky, V. I.: Das Verhältnis der Substantia reticulo-filamentosa im Knochenmark und im peripheren Blute bei verschiedenen Erkrankungen innerer Organe, Folia haemat. **39**:265 (Dec.) 1929. (*b*) Arjeff, M. J.: Zur Methodik der diagnostischen Punktion des Brustbeines, ibid. **45**:55 (Aug.) 1931. (*c*) Barta, I.: Die Bedeutung der Sternalpunktion bei Anämien und über die Beeinflussung des Knochenmarkes durch Leberbehandlung, Deutsches Arch. f. klin. Med. **171**: 565 (Sept. 21) 1931. (*d*) Tuschinsky, M. D., and Kotlarenko, B. N.: Ueber Knochenmarkveränderungen bei Flecktyphus mit Bemerkungen zur Methodik der diagnostischen Punktion des Sternalmarks und der Anfertigung von Knochenmarkpunktatpräparaten, Folia haemat. **46**:235 (Feb.) 1932. (*e*) Tempka, T., and Braun, B.: Das morphologische Verhalten des Sternumpunktates in verschiedenen Stadien der perniziösen Anämie und seine Wandlungen unter dem Einflusse der Therapie, ibid. **48**:355 (Nov.) 1932.

7. Holmes, W. F., and Broun, G. O.: Clinical Study of Bone Marrow by the Method of Sternal Puncture, Proc. Soc. Exper. Biol. & Med. **30**:1306 (June) 1933.

8. Broun, G. O.: Personal communication to the author.

The oxalated marrow can be used for any type of hematologic examination which can be done on oxalated blood.[9]

This technic was developed by an analysis of each step in the procedure, as indicated in the following paragraphs.

Broun [8] felt that the procedure caused so little pain that an anesthetic was hardly necessary. However, by the use of procaine hydrochloride all sensation except that of pressure during the insertion of the needle and a peculiar drawing pain during aspiration of the marrow is eliminated. The pain is slight and entirely localized if 2 cc. or less is slowly aspirated. Rapid withdrawal of larger amounts may cause considerable discomfort, often referred to the lower end of the sternum or to the upper extremities.

A full length spinal puncture needle was used by Arinkin [5b] and others, but we found that a shorter needle, similar to that suggested by Tuschinsky and Kotlarenko,[6d] is more convenient and less likely to break. Since Arjeff [6b] found the anterior lamina of the sternum thicker than the posterior lamina, he devised a special needle with an adjustable guard for limiting the depth of penetration. We found that by inserting the needle at an angle and by bracing the fingers against the chest the possibility of going entirely through the sternum is practically eliminated.

Various investigators have chosen different sites for the puncture. Arinkin [5b] punctured the anterior lamina of the manubrium directly. Tuschinsky and Kotlarenko [6d] penetrated the body of the sternum slightly to the right of the midline at the level of the third rib, with the needle at an angle of 45 degrees. Broun [8] suggested entering the sternomanubrial junction, and we have found this to be the most satisfactory procedure because less pressure is required to enter the marrow cavity. However, if the sternomanubrial junction is not readily found, the needle may be forced through the anterior lamina of the body of the sternum by the application of more pressure.

Several authors have reported inability to obtain bone marrow owing to a marked thickness of the anterior lamina of the bone or to lack of depth of the bone marrow cavity. Arinkin [5b] noted that persons with wide sternal bones are likely to have small marrow cavities. We have had five failures in sixty-two attempts to obtain biopsy specimens. The failures occurred in our early attempts, and may be ascribed to inexperience and timidity. We found that one gains confidence by practice on cadavers.

9. (*a*) Osgood, E. E.; Haskins, H. D., and Trotman, F. E.: A Uniform System of Hematologic Methods for Use with Oxalated Venous Blood, J. Lab. & Clin. Med. **16**:476 (Feb.) 1931. (*b*) Osgood, E. E., and Haskins, H. D.: A Textbook of Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Company, 1931, p. 344.

Most authors did not mention the use of an anticoagulant, but made direct smears immediately. Following Broun's [8] suggestion, we at first aspirated the bone marrow directly into a sterile 2.5 per cent solution of sodium citrate. When unsatisfactory preparations were secured by this technic, we tried centrifugation and also mixing with the patient's blood serum, as suggested by Isaacs.[10] Because of our previous experience with oxalated venous blood,[9] we tried powdered potassium oxalate as an anticoagulant for the bone marrow and found it to give the most satisfactory preparations. This method is simpler and more convenient than the others tried, because it is not necessary to use the marrow immediately, to centrifugate it or to obtain the patient's serum. The preparation also permits hematologic studies other than examination of stained smears.

RESULTS

Differential, peroxidase and reticulocyte counts were made on the oxalated marrow and on oxalated venous blood taken at about the same time. Using the same technic as for blood, thin smears were made on glass slides and stained with Wright's stain, using a buffer phosphate solution with a p_H of 6.4. Five hundred nucleated cells were counted, including normoblasts, megaloblasts, megalokaryocytes and degenerating cells, and the percentages were calculated. The details of cellular morphology in the preparations of bone marrow were as clearly defined as in the best preparations obtained from blood (figs. 1, 2 and 3).

Peroxidase stains were prepared by a modified Washburn technic.[11] From 200 to 500 cells were counted.

The reticulocytes were stained with 1 per cent brilliant cresyl blue in an 0.85 per cent solution of sodium chloride; [12] thin smears were made and the reticulocytes in 1,000 red cells were counted.

Cell Counts in Bone Marrow and Blood of Normal Subjects.—The results of our studies of the venous blood and sternal marrow of twenty-eight healthy male medical students are given in table 1. It is noteworthy that the range of variation in the differential cell counts of the marrow was little greater than that of the blood. As one would expect, the segmented granulocytes were less numerous and the staff cells were much more numerous in the marrow than were the corresponding cells in the blood. Some metamyelocytes and a few of each of the less mature granulocytes were found in the marrow, while similar cells were absent from the blood. The lymphocytes were definitely less

10. Isaacs, R.: Alteration of Tissue Cells in the Blood Stream, Science **68:** 547 (Nov. 30) 1928.

11. Osgood and Haskins.[9b]

12. Osgood, E. E., and Wilhelm, Mable M.: Reticulocytes, J. Lab. & Clin. Med. **19:**1129 (July) 1934.

TABLE 1.—*Differential Counts on Sternal Marrow and Venous Blood of Twenty-Eight Normal Persons* *

Case Number	Red Blood Cells, Millions	Hemoglobin, Gm.	White Blood Cells	Segmented Neutrophils	Segmented Eosinophils	Segmented Basophils	Neutrophil Staff Cells	Eosinophil Staff Cells	Basophil Staff Cells	Neutrophil Metamyelocytes	Eosinophil Metamyelocytes	Neutrophil Myelocytes	Promyelocytes, Type I	Promyelocytes, Type II	Myeloblasts	Lymphocytes	Monocytes	Normoblasts	Megaloblasts	Disintegrating Cells	Reticulocytes†	Myeloid-Erythroblast Ratio
1	....	.....	.....	15.4	...	...	22.6	0.8	...	6.8	0.8	0.8	2.4	3.0	0.4	11.0	0.6	13.0	1.4	21.0	1.9	3.68:1
	5.73	17.14	9,650	**44.0**‡	**3.0**		**4.0**									**45.0**	**2.0**				**2.4**	
2	....	.....	.....	13.0	0.6	0.2	30.8	1.0	...	6.8	0.4	0.4	2.6	2.2	0.4	12.6	0.8	8.6	0.6	18.4	1.2	6.34:1
	4.94	15.69	7,800	**58.0**	**2.0**	**1.0**	**6.0**									**33.0**					**1.2**	
3	....	.....	.....	14.0	0.4	...	24.2	1.0	...	7.0	1.2	1.0	3.0	1.0	0.8	12.4	1.0	14.8	1.0	16.8	2.1	3.68:1
	5.29	14.46	9,350	**53.0**												**41.0**	**6.0**				**3.6**	
4	....	.....	.....	9.2	0.4	...	24.0	1.0	...	9.0	0.2	1.4	2.0	2.0	0.2	9.8	1.6	18.2	1.6	20.6	2.1	2.49:1
	5.01	15.97	7,000	**45.0**	**2.0**		**5.0**									**46.0**	**2.0**				**2.2**	
5	....	.....	.....	10.8	0.6	...	30.2	0.2	...	9.8	0.4	0.6	3.0	3.8	0.4	8.8	1.6	11.8	2.0	15.4	1.3	4.35:1
	4.41	13.93	11,500	**74.0**	**3.0**											**17.0**	**6.0**				**2.0**	
6	....	.....	.....	7.4	...	...	28.8	...	...	7.6	1.0	1.0	1.6	1.2	...	10.4	1.2	12.2	...	27.2	1.8	3.98:1
	4.40	13.52	9,750	**43.0**	**1.0**											**47.0**	**9.0**				**1.6**	
7	....	.....	.....	9.0	1.0	...	26.2	1.4	...	8.4	1.2	0.6	2.2	2.2	1.2	12.4	1.8	10.8	1.4	20.2	2.3	4.37:1
	5.45	18.52	8,300	**59.0**	**2.0**	**1.0**										**32.0**	**4.0**				**1.6**	
8	....	.....	.....	13.6	...	0.2	21.4	0.8	...	6.2	0.2	0.4	1.0	1.2	0.2	9.6	1.2	20.0	1.4	22.6	1.4	2.10:1
	4.77	12.70	9,500	**55.0**												**45.0**					**2.4**	
9	....	.....	.....	11.6	1.0	...	21.0	1.0	...	8.0	2.0	1.4	3.4	2.2	0.8	4.8	1.2	12.8	3.0	25.2	1.8	3.32:1
	5.00	15.18	6,700	**45.0**												**51.0**	**4.0**				**1.0**	
10	....	.....	.....	13.8	0.4	0.2	23.4	...	...	8.0	0.4	1.4	0.8	0.8	0.6	10.0	1.6	13.0	1.6	24.4	1.7	3.41:1
	5.75	18.52	9,700	**52.0**												**47.0**	**1.0**				**1.8**	
11	....	.....	.....	17.2	0.6	0.2	16.8	0.6	...	5.2	0.4	0.4	0.6	1.6	...	11.2	1.2	18.0	1.6	23.8	1.8	2.22:1
	4.69	12.86	9,050	**38.0**	**2.0**											**58.0**	**2.0**				**1.4**	
12	....	.....	.....	15.2	0.8	...	20.2	1.4	...	7.8	1.0	0.8	0.8	1.6	...	3.6	...	16.0	1.8	31.8	1.7	2.79:1
	4.32	13.31	6,300	**58.0**	**3.0**											**34.0**	**5.0**				**0:6**	
13	....	.....	.....	22.4	0.8	...	15.8	0.2	...	8.8	...	0.4	0.4	1.0	...	5.2	...	16.6	0.8	27.4	1.4	2.86:1
	4.53	13.91	12,250	**65.0**	**2.0**	**1.0**	**7.0**									**21.0**	**4.0**					

14	....	.....	.....	8.6	0.6	...	29.8	1.0	0.2	8.8	0.6	0.4	2.2	1.4	0.4	8.4	2.2	13.6	3.8	18.0	2.2	3.10:1
	5.27	16.26	8,950	**57.0**												**29.0**	**4.0**				**2.4**	
15	....	.....	.....	23.2	...	0.2	16.2	0.4	...	1.8	...	...	...	0.2	...	13.6	2.2	6.6	0.4	31.2	1.6	6.28:1
	5.88	15.80	8,200	**38.0**	**1.0**		**1.0**									**59.0**					**1.7**	
16	....	.....	.....	10.2	...	...	16.0	0.6	0.2	8.0	0.8	1.0	1.6	1.6	0.4	14.0	2.0	11.2	1.6	29.4	1.7	3.15:1
	5.14	15.69	6,250	**57.0**												**41.0**	**2.0**				**1.4**	
17	....	.....	.....	13.8	0.4	...	33.0	1.4	...	7.8	1.0	0.8	1.0	1.0	0.4	9.8	3.6	6.6	1.4	17.8	1.5	7.57:1
	5.07	14.15	8,850	**74.0**	**3.0**		**2.0**									**17.0**	**4.0**				**0.6**	
18	....	.....	.....	14.2	0.8	0.2	26.4	1.4	...	9.8	0.2	0.6	0.4	1.4	...	12.0	2.4	5.4	1.4	23.8	2.0	8.14:1
	4.80	16.55	13,650	**74.0**												**21.0**	**5.0**				**1.8**	
19	....	.....	.....	10.4	...	...	22.0	0.6	0.6	7.4	0.4	0.4	0 2	0.2	0.6	10.6	0.4	17.2	4.2	24.8	1.9	2.00:1
	4.59	14.04	7,450	**49.0**												**48.0**	**3.0**				**1.4**	
20	....	.....	.....	13.6	0.6	0.2	25.2	1.4	...	8.0	1.6	2.6	4.0	1.8	0.8	11.4	4.4	7.4	0.8	14.4	2.2	7.34:1
	5.68	19.37	8,700	**61.0**	**1.0**	**1.0**										**35.0**	**2.0**				**1.4**	
21	....	.....	.....	7.4	...	...	28.4	0.6	0.2	6.2	0.6	1.2	1.8	0.6	0.4	13.6	3.8	13.4	2.2	19.0	2.1	3.42:1
	5.14	16.77	7,100	**67.0**	**1.0**											**30.0**	**2.0**				**2.4**	
22	....	.....	.....	12.0	0.6	0.2	20.6	0.8	...	8.0	0.8	0.6	1.0	1.4	0.2	13.0	2.2	12.4	3.0	22.8	1.9	3.00:1
	4.96	16.94	6,650	**63.0**	**2.0**											**32.0**	**3.0**				**1.4**	
23	....	.....	.....	11.8	0.2	...	27.6	1.6	...	9.6	1.2	0.6	2.0	1.2	0.6	8.6	3.8	10.6	2.4	15.6	5.2	4.35:1
	5.20	17.47	7,900	**48.0**	**7.0**	**1.0**	**1.0**									**38.0**	**5.0**				**1.0**	
24	....	.....	.....	12.2	0.2	...	25.8	0.6	0.2	6.8	0.2	0.2	1.2	1.6	...	14.6	4.2	7.6	1.6	21.4	2.4	5.32:1
	5.18	16.55	9,750	**56.0**	**2.0**											**34.0**	**6.0**			**2.0**	**1.8**	
25	....	.....	.....	18.4	1.0	0.2	27.4	1.2	0.4	6.2	0.6	1.0	2.0	1.8	0.8	10.4	3.0	6.8	0.6	18.6	1.8	8.20:1
	5.12	14.25	5,950	**65.0**												**33.0**	**2.0**				**2.2**	
26	....	.....	.....	14.2	0.4	...	27.4	1.2	...	5.4	0.2	1.6	1.6	1.0	0.8	9.6	3.4	14.1	2.8	15.4	1.3	3.81:1
	5.49	16.98	9,150	**63.0**	**2.0**		**1.0**									**32.0**	**2.0**				**1.6**	
27	....	.....	.....	14.2	0.4	0.2	26.6	1.2	...	7.6	0.4	1.6	2.8	1.4	0.8	9.4	2.8	15.4	1.4	12.8	2.5	3.40:1
	5.70	17.94	7,750	**75.0**			**1.0**									**20.0**	**4.0**				**1.2**	
28	....	.....	.....	13.8	0.8	0.2	18.6	0.6	...	6.4	0.2	0.8	1.4	1.0	1.0	16.0	3.4	13.2	2.0	19.8	1.8	2.94:1
	5.00	15.83	7,750	**51.0**	**1.0**		**2.0**									**42.0**	**4.0**				**1.2**	
Average	....	.....	.....	13.3	0.4	0.1	24.1	0.8	0.1	7.4	0.6	0.8	1.7	1.5	0.4	10.6	2.1	12.4	1.7	20.8	1.9	3.61:1
	5.09	15.72	8,600	**56.7**	**1.4**	**0.2**	**1.0**									**36.0**	**3.3**				**1.7**	
Maximum	....	.....	.....	25.2	1.0	0.2	33.0	1.6	0.6	9.8	2.0	2.6	4.0	3.8	1.2	16.0	4.2	20.0	4.2	31.8	5.2	8.20:1
	5.88	19.37	13,650	**75.0**	**7.0**	**1.0**	**7.0**									**59.0**	**6.0**			**2.0**	**3.6**	
Minimum	....	.....	.....	7.4	0.0	0.0	15.8	0.0	0.0	1.8	0.0	0.0	0.0	0.0	0.0	4.8	0.0	5.4	0.0	12.8	1.2	2.00:1
	4.32	12.70	5,950	**36.0**	**0.0**	**0.0**	**0.0**									**17.0**	**0.0**			**0.0**	**0.6**	

* The figures for each type of cell are given in per cent. The percentages of basophil myelocytes, Türk cells, plasma cells, mitotic cells and megalokaryocytes were so small that they are omitted.

† The reticulocytes are in per cent of red cells.

‡ The figures in bold face represent differential counts on blood taken at the time of the bone marrow biopsy.

numerous and the monocytes slightly less numerous in the marrow than in the blood. Degenerating cells, which were included in the differential count, were abundant in the bone marrow and were seldom found in the blood. There was little difference in the reticulocyte count in the bone marrow and in the blood.

With the exception of the mature erythrocyte, the predominant cell in the bone marrow (fig. 1) was the neutrophil staff cell. Segmented neutrophils and normoblasts were next in frequency. A few megaloblasts were present. Türk cells, Marschalko plasma cells and megalokaryocytes were seldom encountered in making the differential count, but were demonstrable, by a careful survey, in almost every preparation. Mitoses in nucleated red cells were occasionally seen. The cellular morphology

Fig. 1.—Bone marrow of a normal healthy man.

was so clearly defined that it was seldom necessary to designate a cell as unclassified. The monocytes and all the cells of the myeloid series, except myeloblasts, gave a positive peroxidase reaction. The ratio of the total myeloid cells to the total nucleated red cells varied from 8.29:1 to 2.00:1 and averaged 3.61 : 1.

Table 2 summarizes, for comparison, all the differential counts available on normal bone marrow obtained by sternal puncture. The apparent discrepancies may be explained by the different criteria for classification of the cells and by the fact that our differential counts were the only ones to include disintegrating cells. It is noteworthy that all who have reported reticulocyte counts found approximately equal percentages in bone marrow and in blood. Comparison of the myeloid-erythroblast ratios shows them to agree.

Cell Count in Bone Marrow and Blood of Persons with Pathologic Conditions.—The results of studies of the marrow and blood in twenty-six cases representing fifteen different disorders of the blood and blood-forming organs are summarized in table 3.

REPORT OF CASES

CASE 1.—A man, aged 28, was selected as a normal subject, but study of the marrow revealed a definite increase in the number of eosinophil cells of all types. Eosinophilia was also found in the blood, for which no cause was discovered.

TABLE 2.—*Summary of Reported Differential Cell Counts on Sternal Marrow from Normal Persons*

	Arinkin	Holmes and Broun[7]	Tempka and Braun*	Young and Osgood
	Range	Average	Range	Range
Number of cases	?	7	3	28
Segmented neutrophils	41.0 to 55.0	17.4	16.2 to 20.3	7.4 to 25.2
Segmented eosinophils	0.6 to 4.0	1.0	0.7 to 2.5	0.0 to 1.0
Segmented basophils	0.0 to 0.7	0.3	0.2 to 0.3	0.0 to 0.2
Neutrophil staff cells†	.....	14.0	17.0 to 22.5	15.8 to 33.0
Eosinophil staff cells	.....	....	0.5 to 1.0	0.0 to 1.6
Basophil staff cells	.....	....	0.0 to 0.2	0.0 to 0.6
Neutrophil metamyelocytes	1.4 to 3.4	6.7	14.3 to 16.2	1.8 to 9.8
Eosinophil metamyelocytes	0.3 to 1.0	....	0.3 to 3.7	0.0 to 2.0
Basophil metamyelocytes	.....	....	0.0 to 0.2	
Neutrophil myelocytes	4.5 to 8.6	7.0	12.7 to 13.3	0.0 to 2.6
Eosinophil myelocytes	0.3 to 1.0	....	1.5 to 2.7	0.0 to 0.4
Basophil myelocytes	.....	....	0.0 to 0.3	
Promyelocytes, type I	.....	....	.....	0.0 to 4.0
Promyelocytes, type II	1.0 to 2.8	....	3.7 to 6.8	0.0 to 3.8
Myeloblasts (stem cell)	1.0 to 2.4	2.4	4.6 to 7.0	0.0 to 1.2
Lymphocytes	7.3 to 16.5	24.9	2.6 to 3.3	4.8 to 16.0
Monocytes (reticulo-endothelial)	2.1 to 9.3	9.0	0.5 to 0.8	0.0 to 4.2
Normoblasts	5.7 to 16.0	6.9	13.3 to 16.6	5.4 to 20.0
Megaloblasts	0.8 to 2.9	5.2	.....	0.0 to 4.2
Megalokaryocytes	0.6 to 6.1	....	2.2 to 4.0	0.0 to 0.2
Plasma cells (Türk cells included)	0.3 to 0.9	....	0.3 to 1.6	0.0 to 1.0
Disintegrating cells	.....	....	.....	12.8 to 31.8
Reticulocytes‡	0.8 to 1.4	....	0.8	1.2 to 5.2
Myeloid-erythroblast ratio§	7.70:1 to 4.17:1	4.86:1	5.83:1 to 5.39:1	8.29:1 to 2.00:1

* Nucleated erythrocytes were not included in the differential count. These figures are calculated from Tempka and Braun's data.

† Arinkin did not differentiate staff cells from the segmented cells. The percentage of reticulocytes was reported by Pokrovsky.[6a]

‡ The figures for reticulocytes are in per cent of red cells.

§ The ratio was calculated from the authors' data.

CASE 2.—A youth, aged 16, had neutrophilic leukocytosis, an increase in the number of staff cells caused by bronchopneumonia and empyema due to Streptococcus haemolyticus. The marrow showed an increase in the number of immature neutrophils of all types, promyelocytes, myeloblasts and plasma cells.

CASE 3.—A girl, aged 17, had unexplained leukopenia (count, from 1,850 to 6,500 cells) of at least six months' duration. The diagnosis of aleukemic myelosis was being considered, but the only variation from the normal in the bone marrow was a decrease in the number of segmented neutrophils. The patient remained under observation and seemed to have physiologic leukopenia of the type described by Roberts and Kracke.[13]

13. Roberts, S. R., and Kracke, R. R.: Agranulocytosis: Its Classification; Cases and Comments Illustrating the Granulopenic Trend from 8,000 Blood Counts in the South, Ann. Int. Med. **5**:40 (July) 1931.

TABLE 3.—*Differential Count on Sternal Marrow and Venous Blood of Twenty-Six Patients with Pathologic Conditions* *

Case Number	Diagnosis	Red Blood Cells, Millions	Hemoglobin, Gm.	White Blood Cells	Segmented Neutrophils	Segmented Eosinophils	Segmented Basophils	Neutrophil Staff Cells	Eosinophil Staff Cells	Basophil Staff Cells	Neutrophil Metamyelocytes	Eosinophil Metamyelocytes	Neutrophil Myelocytes	Promyelocytes, Type I	Promyelocytes, Type II	Myeloblasts	Lymphocytes	Monocytes	Normoblasts	Megaloblasts	Disintegrating Cells	Reticulocytes	Myeloid-Erythroblast Ratio
1	Eosinophilia	....	.....	.....	**26.4†**	**4.8**	**0.4**	17.0	**2.0**	...	6.4	1.4	**2.8**	0.6	3.8	0.6	5.4	...	7.6	2.4	17.2	4.8	6.68:1
		4.79	14.46	8,250	**54.0**	**15.0**	**3.0**										**25.0**	**3.0**				**1.2**	
2	Streptococcic pneumonia	....	.....	.....	12.0	0.4	...	**34.8**	1.0	...	**12.0**	1.0	2.0	**4.4**	**5.0**	**1.4**	6.8	0.2	3.0	2.2	9.4	**0.9**	**14.20:1**
		5.16	14.25	27,900	**62.0**			**24.0**									**9.0**	**5.0**					
3	Leukopenia	....	.....	.....	**2.4**	0.8	...	22.2	0.6	...	3.4	0.2	...	1.2	3.8	0.2	5.8	0.2	**23.6**	3.4	32.8	1.2	**1.29:1**
		4.77	11.35	4,650	**61.0**			**4.0**									**30.0**	**5.0**				**1.6**	
4	Aplastic anemia	....	.....	.....	**0.0**	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	
		1.43	3.80	1,350	**24.0**												**76.0**					**0.1**	
5	Carcinoma of stomach	....	.....	.....	**7.0**	0.2	...	19.8	0.2	...	7.0	...	0.8	1.0	0.4	...	16.0	0.2	**30.4**	3.4	13.2	3.9	**1.07:1**
		2.67	3.53	7,300	**60.0**		**1.0**										**30.0**	**2.0**			**7.0**		
6	Uterine fibroids	....	.....	.....	17.8	...	...	31.0	0.6	...	8.0	...	1.6	1.2	1.0	0.4	7.2	0.6	**21.0**	1.8	7.4	4.6	2.70:1
		2.90	4.46	3,550	**52.0**	**2.0**		**3.0**									**40.0**	**3.0**				**2.3**	
7	Congenital syphilis	....	.....	.....	**1.4**	...	...	**6.4**	...	...	2.6	...	0.2	0.8	2.2	...	10.8	1.0	**50.4**	**5.0**	19.6	4.4	**0.24:1**
		1.63	4.10	2,800	**36.0**			**3.0**									**60.0**	**1.0**	**1.0**	**1.0**		**3.0**	
8	Tertiary syphilis	....	.....	.....	16.0	0.6	0.4	17.2	0.6	...	3.8	0.4	0.4	0.8	1.2	0.6	**20.6**	2.4	12.0	1.6	18.2	0.9	3.09:1
		3.29	6.98	4,850	**52.0**												**43.0**	**5.0**				**2.4**	
9	Still's disease	....	.....	.....	21.8	0.8	...	31.6	**1.8**	...	5.8	0.4	**3.0**	...	**8.2**	...	7.8	...	9.4	2.4	7.4	1.9	6.05:1
		3.64	8.82	6,050	**55.0**	**1.0**											**31.0**	**13.0**					
10	Nephritis	....	.....	.....	8.6	0.2	...	**41.2**	0.8	...	9.8	0.6	1.4	0.8	0.8	**1.4**	6.6	1.0	9.0	0.4	16.2	**5.7**	6.98:1
		3.37	9.08	9,570	**52.0**			**10.0**									**22.0**	**6.0**			**6.0**		
11	Nephritis	....	.....	.....	8.2	...	...	18.4	0.2	...	6.0	...	0.6	0.8	1.4	...	6.2	0.4	**37.4**	2.2	16.8	**15.9**	**0.90:1**
		2.01	5.44	15,500	**79.0**												**17.0**				**3.0**	**8.0**	
12	Lead poisoning	....	.....	.....	8.6	0.4	...	24.0	1.0	...	7.6	1.2	1.8	0.8	1.4	0.8	7.0	2.2	**27.6**	**4.4**	9.8	11.1	**1.25:1**
		4.15	11.19	13,600	**59.0**	**2.0**		**5.0**									**32.0**	**2.0**				**7.6**	
13	Hemolytic icterus	....	.....	.....	**7.0**	0.4	0.2	18.2	0.2	...	6.6	0.8	1.4	**4.2**	2.8	1.2	5.4	0.2	**26.2**	**10.6**	13.2	**8.7**	**1.17:1**
		4.98	14.57	9,650	**50.0**	**3.0**	**1.0**										**46.0**					**8.0**	

14	Banti's disease	...	.....	.....	**4.2**	0.2	...	18.2	...	...	9.2	0.2	**4.6**	...	**7.8**	0.6	**1.0**	...	**28.8**	**14.2**	9.6	...	**1.05:1**
		3.63	9.80	3,550	**64.0**			**2.0**									**30.0**	**2.0**			**2.0**		
15	Pernicious anemia	....	.....	.....	**4.6**	**1.6**	...	**6.4**	0.8	...	**1.2**	0.2	...	1.4	2.4	1.2	9.2	...	**24.2**	**16.8**	30.0	**9.6**	2.07:1
		1.20	5.65	3,050	**49.0**			**1.0**									**40.0**		**7.0**	**3.0**	**10.0**	**2.4**	
		2.63	8.82	6,150	15.4	0.2	...	**10.6**	...	...	2.2	...	...	0.4	0.8	0.2	15.6	0.6	**24.2**	2.0	27.8	2.4	**1.13:1**
					61.0		**3.0**	**3.0**									**29.0**	**4.0**				**1.0**	
16	Pernicious anemia	....	.....	.....	15.6	**1.4**	...	**6.6**	0.4	0.4	2.6	...	...	1.4	**7.2**	0.6	6.2	...	10.6	**6.4**	41.8	1.2	2.13:1
		1.89	5.66	3,850	**64.0**		**1.0**										**35.0**						
					11.0	0.6	0.4	17.2	...	...	5.6	...	0.6	1.4	1.0	0.4	**3.2**	1.0	**29.6**	**6.0**	21.0	**16.3**	**1.07:1**
		2.10	6.14	3,700	**70.0**		**1.0**										**28.0**	**1.0**				**7.6**	
17	Pernicious anemia	....	.....	.....	8.0	**1.2**	0.2	**8.4**	1.0	...	4.0	0.2	0.8	0.8	1.6	0.2	14.0	0.2	17.6	**17.4**	24.0	1.2	**0.75:1**
		1.53	5.70	5,450	**62.0**	**1.0**											**33.0**	**4.0**				**1.1**	
18	Pernicious anemia	....	.....	.....	13.8	0.6	...	13.4	1.2	...	4.2	0.4	0.6	1.0	2.0	...	**17.6**	0.6	12.6	**10.8**	21.0	2.3	**1.63:1**
		1.69	7.05	2,800	**37.0**	**1.0**		**2.0**									**57.0**	**3.0**					
19	Hodgkin's disease	....	.....	.....	23.8	1.2	0.2	24.4	0.6	...	2.6	0.8	0.2	0.4	0.2	...	**17.8**	2.2	5.4	1.2	17.0	1.2	8.24:1
		4.21	12.20	8,900	**71.0**												**24.0**	**5.0**					
20	Hodgkin's disease	....	.....	.....	22.0	0.8	...	**35.2**	1.2	...	8.4	0.8	1.6	3.0	3.6	0.6	5.4	1.6	**3.8**	0.8	10.2	3.7	**16.80:1**
		4.21	11.04	16,950	**92.0**												**5.0**	**2.0**			**1.0**		
21	Myelogenous leukemia	....	.....	.....	**7.2**	**1.4**	**0.6**	28.0	**2.0**	**1.4**	**13.8**	**4.0**	**6.8**	**13.6**	**8.0**	**1.8**	**1.6**	0.2	**2.0**	...	5.2	3.5	**35.10:1**
		3.02	8.62	260,000	**23.0**	**2.0**	**3.0**	**28.0**	**4.0**		**2.0**		**1.0**		**22.0**				**2.0**	**2.0**		**5.0**	
					4.6	...	...	23.6	1.0	0.2	**14.0**	**3.0**	**10.8**	**6.6**	**16.6**	**2.0**	**1.6**	0.2	**1.8**	0.4	10.0	...	**34.70:1**
		3.75	10.21	246,000	**23.0**	**5.0**	**3.0**	**30.0**			**12.0**		**16.0**		**9.0**		**2.0**						
22	Myelogenous leukemia	....	.....	.....	10.2	0.2	**0.6**	25.0	0.2	...	9.2	0.4	1.2	3.0	1.6	0.4	6.0	0.8	18.8	1.4	20.8	3.4	2.57:1
		4.69	13.74	6,300	**47.0**		**3.0**	**2.0**									**37.0**	**5.0**			**6.0**		
23	Myelogenous leukemia	....	.....	.....	13.4	**0.2**	...	26.2	0.4	...	5.8	0.2	1.2	2.0	1.4	**1.6**	5.0	1.6	**20.2**	**5.0**	15.2	2.4	2.09:1
		3.90	10.13	7,900	**70.0**	**2.0**											**19.0**	**8.0**				**1.2**	
					14.0	0.2	...	10.6	0.8	0.2	3.4	...	0.4	1.8	2.8	**24 2**	4.0	1.2	4.4	0.4	20.0	**0.8**	**12.25:1**
		3.98	10.79	25,250	**54.0**			**3.0**			**2.0**				**11.0**	**24.0**					**6.0**		
24	Monocytic leukemia	....	.....	.....	**0.0**	...	...	**0.4**	...	...	**0.0**	...	...	...	...	...	7.4	**42.0‡**	....	...	**50.0**	**0.3**	
		4.01	11.22	5,050	**0.8**			**1.2**			**0.2**						**42.6**	**27.6**	**0.2**		**40.4**		
25	Xanthomatosis	....	.....	.....	**0.0**	...	...	**7.4**	...	...	5.6	...	**5.6**	0.6	**8.0**	0.2	**42.6**	...	6.4	3.8	19.2	...	2.68:1
		3.44	8.79	9,500				**48.0**							**1.0**		**50.0**	**1.0**					
26	Multiple myeloma§	....	.....	.....	**35.0**	0.4	**0.4**	**14.0**	...	...	3.2	...	0.4	...	1.8	...	**19.6**	0.2	**4.2**	2.6	13.5	1.2	8.12:1
		1.74	5.46	7,060	**54.0**	**3.0**		**2.0**									**32.0**	**7.0**					

* The figures for each type of cells are given in per cent. The percentages of basophil myelocytes, Türk cells, plasma cells, mitotic cells and megalokaryocytes were so small that they are omitted.

† The figures in bold face in the first line represent deviations from the normal, and those in bold face in the second line represent differential counts on specimens of blood taken at the time the biopsy on the bone marrow was made.

‡ Monocytes, 42 per cent, include: mature monocytes, 0.2 per cent; promonocytes, 10.0 per cent, and monoblasts, 31.8 per cent.

§ Two and six-tenths per cent plasma cells were present.

CASE 4.—A man, aged 62, had aplastic anemia following the administration of neoarsphenamine. Practically no nucleated cells were found in the marrow, and reticulocytes were very scarce.

CASE 5.—A woman, aged 40, had anemia due to chronic hemorrhage secondary to advanced carcinoma of the stomach. The only deviations from the normal count in the marrow were a marked increase in the number of normoblasts and microcytosis, hypochromia and poikilocytosis similar to those observed in the blood.

CASE 6.—A woman, aged 39, had chronic hemorrhagic anemia due to uterine bleeding secondary to fibromyomas. The marrow showed an increase in the number of normoblasts similar to the increase in case 5.

CASE 7.—A girl, aged 5 years, had severe anemia with leukopenia. Clinically, aplastic anemia, aleukemic myelosis and anemia of congenital syphilis were considered. The marrow showed a striking increase in normoblasts, a moderate increase in the number of megaloblasts and a decrease in the number of segmented granulocytes and staff cells. This picture was incompatible with a diagnosis of aplastic anemia or aleukemic myelosis. A report of 4 plus Kolmer and Kahn reactions of the child and of her mother confirmed the diagnosis of congenital syphilis. The patient made a rapid recovery following transfusions of blood and antisyphilitic therapy.

CASE 8.—A man, aged 50, with mild anemia, tertiary syphilis and hypertension, had been treated for pernicious anemia in a veterans' hospital. The marrow was essentially normal, and the blood findings and the amount of free hydrochloric acid in the gastric contents excluded a diagnosis of pernicious anemia.

CASE 9.—A man, aged 19, had mild anemia. A clinical diagnosis of Still's disease was made. The only noteworthy change in the marrow was an increase in the number of segmented neutrophils and staff cells.

CASE 10.—A boy, aged 5 years, had acute glomerular nephritis with moderate anemia. The marrow showed an increase in the number of staff cells, mitotic normoblasts and reticulocytes.

CASE 11.—A woman, aged 34, had marked anemia secondary to chronic glomerular nephritis. Her marrow showed marked increase in the number of normoblasts and reticulocytes without an increase in the number of megaloblasts.

CASE 12.—A man, aged 36, with an acute abdominal disturbance caused by chronic lead poisoning, had only moderate anemia, but there were many stippled cells and reticulocytes in the blood. The marrow (fig. 2) showed a moderate increase in the number of normoblasts and megaloblasts and large numbers of stippled cells and reticulocytes.

CASE 13.—A man, aged 27, had laboratory and clinical findings typical of familial hemolytic icterus, except for the absence of anemia. The marrow showed an increase in the number of normoblasts, megaloblasts and reticulocytes and microcytosis of the mature erythrocytes.

CASE 14.—A man, aged 52, had marked splenomegaly and mild anemia. Clinical opinion differed as to whether the diagnosis should be Gaucher's disease or Banti's disease. Absence of Gaucher cells from the marrow favored the diagnosis of Banti's disease, which was confirmed by splenectomy and, later, by necropsy. The marrow showed a marked increase in the number of megaloblasts and a moderate increase in the number of normoblasts, myelocytes and metamyelocytes.

CASES 15, 16, 17 AND 18.—Four men, aged 47, 69, 67 and 74, respectively, had pernicious anemia. Before treatment, all had severe anemia with a normal reticulocyte count. The bone marrow, at this time, showed a marked increase in the number of megaloblasts (fig. 3), and tended toward a decrease in the number of granulocytes. The marrow of the patient is case 15 showed a moderate increase in the number of normoblasts and reticulocytes. While the patients were under treatment, studies of the marrow were repeated for comparison with the previous findings. The marrow of the patient in case 16, taken at the height of the increase in the number of reticulocytes in the blood, showed a great increase in the number of reticulocytes and normoblasts without much change in the number of megalo-

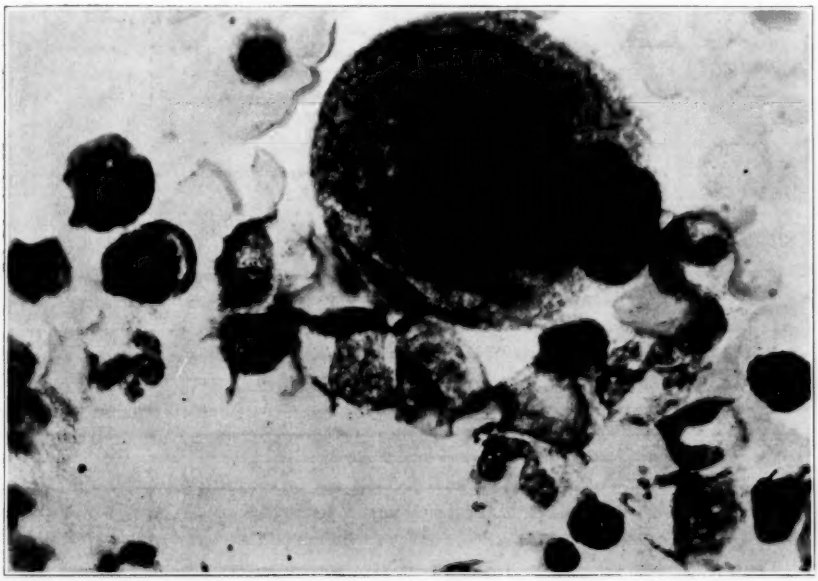

Fig. 2 (case 12).—Bone marrow of a patient with lead poisoning, showing a typical megalokaryocyte. Note the megaloblasts.

blasts. The marrow of the patient in case 15, taken ten days after the peak of the increase in the number of reticulocytes, showed a marked decrease in the number of megaloblasts.

CASES 19 and 20.—Two men, aged 28 and 17, respectively, had typical Hodgkin's disease. The picture in the marrow was essentially normal.

CASES 21, 22 AND 23.—Three women, aged 47, 44 and 49, respectively, had chronic myelogenous leukemia. In all of them, the blood reflected the picture in the bone marrow. The marrow of the patient in case 21 before treatment showed a marked increase in the number of immature granulocytes. Twenty days after 3,216 mg. hours of radium was applied over the spleen, the pictures in the blood and marrow were little altered. Studies of the marrow were done in cases 22 and 23 at a time when the blood picture had returned to normal after prolonged

roentgenotherapy. It is interesting to note that the pictures in the marrow were also normal. In case 23, a second study of the marrow was done during a terminal myeloblast crisis. Both the blood and the bone marrow showed a striking increase in the number of myeloblasts.

CASE 24.—A girl, aged 7 years, had acute subleukemic monocytic leukemia. The marrow showed a striking picture, with immature cells of the monocytic series replacing the myeloid and erythroid cells.

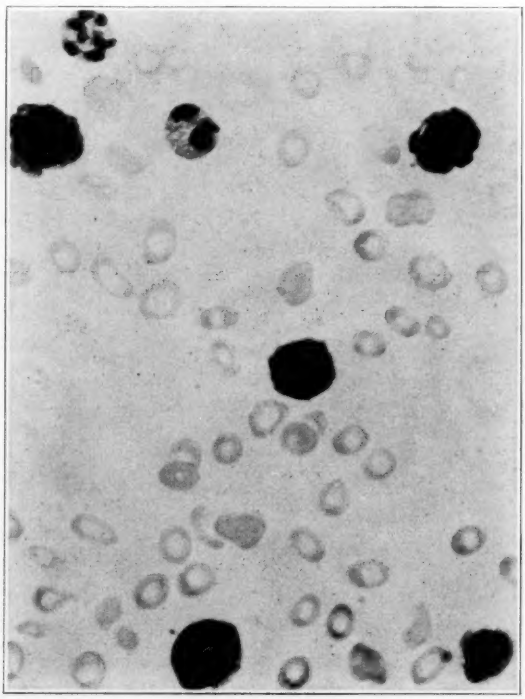

Fig. 3 (case 17).—Bone marrow of a patient with pernicious anemia, showing four typical megaloblasts and a multisegmented neutrophil.

CASE 25.—A boy, aged 5 years, had xanthomatosis of the Hand-Schüller-Christian type. Sternal puncture was done shortly after death. The marrow showed no typical foam cells. That the sternal marrow was free from xanthomatous infiltration, although it was present in the marrow of other bones and in many other tissues, was shown at necropsy.

CASE 26.—A woman, aged 51, had Bence-Jones protein in the urine and multiple defects of the bone. The marrow showed an increase in the number of plasma cells, which favored a diagnosis of multiple myeloma rather than that of a metastatic malignant process.

COMMENT

Although there are certain limitations to the study of bone marrow obtained by the method of sternal puncture, the method has definite advantages which make it valuable. It aids the experimental hematologist in the study of the origin of blood cells and the physiology of bone marrow and assists the clinician in the solution of some diagnostic problems.

One disadvantage of the method, as pointed out by Peabody [4] and Custer,[13a] is that it fails to show the structural relationships which can be seen in fixed sections of the marrow. Another limitation, which applies to all methods of obtaining bone marrow for biopsy, is that only a small, and not necessarily a representative, sample of the entire supply of marrow of the body is obtained. Patchy lesions, such as occur in multiple myeloma, Gaucher's disease, Niemann-Pick's disease, xanthomatosis and metastatic malignant processes may be missed, as in our case of xanthomatosis (case 25). However, an increase in the number of plasma cells was found in our case of multiple myeloma (case 26), and Sokolowski [14] found typical cells in a case of Gaucher's disease. Our failure to find Gaucher cells in a case of splenomegaly aided us in making a correct diagnosis of Banti's disease. Therefore, the failure to find typical cells does not necessarily exclude the diagnosis of a patchy lesion, but may be a point against such diagnosis.

The possibility suggests itself that the differential counts on the material aspirated by sternal puncture do not represent the true proportion of the cells in the marrow, either because of dilution with blood or because of a tendency of some cells to be more firmly adherent. From our studies it is evident that error from these sources, if it does occur, is so slight and relatively constant that it does not detract from the clinical value of the method. If there were much variation in the cellular content of the material obtained, our differential cell counts on marrow from normal subjects would show a greater variation. The myeloid-erythroblast ratio would be high in the marrow of normal subjects if there were much dilution with blood. Our myeloid-erythroblast ratios (3.61 : 1) fall between those obtained from emulsified, curetted marrow obtained at necropsy by Schilling [15] (1.21 : 1) from ten soldiers and by

13a. Custer, R. P.: Studies on the Structure and Function of Bone Marrow Biopsy, Am. J. M. Sc. **185**:617 (May) 1933.

14. Sokolowski, A.: Basophile kugelförmige Gebilde im Milzpunktate im Verlaufe des Morbus Gaucher und die Bedeutung des Sternumpunktates für die Diagnose dieser Erkrankung, Folia haemat. **46**:281 (Feb.) 1932.

15. Schilling, V.: Das Knochenmark als Organ: II. Die feinere Zytologie des Markparenchyms, Deutsche med. Wchnschr. **51**:344 (Feb. 27) 1925.

Doan and Zerfas [16] (9.66:1) from four persons who died as a result of accidents. Because of the presence of blood in the sinuses, all bone marrow obtained for study, including tissue sections, will show some mixture with blood.

The advantages of obtaining biopsy material by sternal puncture are the accurate definition of the morphologic characteristics of the cells and the simplicity of the technic. The clear definition makes it possible to identify each cell accurately, to trace the histogenesis of each cell type and to determine the stage of maturation at which delivery from the bone marrow into the blood occurs. In our material it was possible to trace the development of the erythrocytes and monocytes, as well as that of the granulocytes, from the most mature cell of the series back to a stem cell morphologically similar to the myeloblast. This conflicts with the view expressed by Piney [17] that the megaloblast is not the precursor of the mature erythrocyte, and with some of the many views, summarized by Forkner,[18] concerning the origin of monocytes. The fact that typical megaloblasts were found in almost every specimen of marrow examined also conflicts with Piney's [17] view that the megaloblast is seen only in pernicious anemia. Our observations on mitosis and the delivery of cells agree with those of Sabin.[19] In tracing the maturation of the granulocytes and erythrocytes, mitotic division was observed in cells at least as mature as myelocytes and normoblasts. The absence of metamyelocytes and normoblasts and the presence of staff cells and reticulocytes in the blood and the presence of all these cells in the bone marrow indicate that delivery of the granulocytes and erythrocytes into the blood normally begins at the stage of the staff cell and reticulocyte.

The picture in the marrow enables the clinician to understand more clearly the mechanism of the production of the changes in the blood in disease. In some instances, study of the bone marrow establishes or confirms a diagnosis, and it is often of assistance in planning rational therapy.

In simple leukopenia and in various types of leukocytosis the blood picture accurately reflects the changes in the bone marrow, as illustrated in cases 1, 2 and 3. The picture in the marrow will, however, differ-

16. Doan, C. A., and Zerfas, L. G.: The Rhythmic Range of White Blood Cells in Human, Pathological Leucopenic and Leucocytic States, with Study of Thirty-Two Human Bone Marrows, J. Exper. Med. **46**:511 (Sept.) 1927.

17. Piney, A.: Nucleated Red Cells Found in Circulation in Pernicious Anemia, J. Path. & Bact. **27**:249 (July) 1924.

18. Forkner, C. E.: Clinical and Pathologic Differentiation of the Acute Leukemias, with Special Reference to Acute Monocytic Leukemia, Arch. Int. Med. **53**:1 (Jan.) 1934.

19. Sabin, Florence R.: The Bone Marrow, Physiol. Rev. **8**:191 (April) 1928.

entiate simple leukopenia from aplastic anemia and aleukemic leukemia and probably from essential granulopenia (agranulocytic angina). It should aid in distinguishing leukocytosis of a leukemoid type from true leukemia.

In cases of anemia, sternal puncture gives much valuable information. In aplastic anemia the diagnosis can be definitely established (case 4), and the first evidence of returning function of the marrow should be readily detectable. An increase in the number of normoblasts is the most characteristic feature of the marrow in anemia due to chronic hemorrhage (cases 5 and 6), infections (cases 7, 8, 9, 10 and 11), toxins (case 12) or hemolytic icterus (case 13). This hyperplasia of the marrow is reflected by evidence of rapid regeneration of the red cells in the blood in lead poisoning (case 12) and in hemolytic icterus (case 13), but such evidence of regeneration is slight or absent in chronic hemorrhage and in infection. In the case of congenital syphilis (case 7) the blood picture suggested aplastic anemia. Brown and Roth [20] and Osgood and Haskins [21] pointed out that the blood picture in anemia of nephritis suggests decreased activity of the bone marrow. This apparent discrepancy between the findings in the blood and those in the marrow supports Witts' [22] statement that "hyperplasia of the marrow is by no means synonymous with increased blood formation, the reaction is often abortive and the cells fail to mature." The finding of numerous stippled erythrocytes in the marrow in lead poisoning (case 12) does not agree with the opinion of Aub and his associates [23] that basophilic stippling does not occur in the marrow. The finding of basophilic stippling in most specimens of bone marrow studied suggests that this is a sign of immaturity, not of degeneration, and can be used, as are polychromatophilia and reticulocytosis, to indicate an increased rate of regeneration of red cells.

In untreated pernicious anemia (cases 15, 16, 17 and 18) the most characteristic change in the marrow is an increase in the number of megaloblasts. This observation agrees with the findings of Peabody [3] in seven cases, of Arinkin [5a] in ten cases, of Barta [6c] in twenty-two cases, of Tempka and Braun [6e] in thirty cases and of Holmes and Broun.[7] As reported by Tempka and Braun, a few multilobulated

20. Brown, G. E., and Roth, G. M.: The Anemia of Chronic Nephritis, Arch. Int. Med. **30**:817 (Dec.) 1922.

21. Osgood, E. E., and Haskins, H. D.: Causes, Classification, and Differential Diagnosis of Anemias, Ann. Int. Med. **5**:1367 (May) 1932.

22. Witts, L. J.: Pathology and Treatment of Anemia (Goulstonian Lectures), Lancet **1**:495 (March 5); 549 (March 12); 601 (March 19) and 653 (March 26) 1932.

23. Aub, J. C.; Fairhall, L. T.; Minot, A. S., and Resnikoff, P.: Lead Poisoning, Medicine **4**:1 (Feb.-May) 1925.

neutrophils and giant staff cells are present. No cell type is specific for pernicious anemia, although as a whole the picture in the marrow has diagnostic value. With treatment, the picture reverts to normal and studies of the marrow add little to the information obtainable from studies of the blood.

Studies of the marrow in Hodgkin's disease (cases 19 and 20) are of no diagnostic value. No support was found for Medlar's [24] view that there is a proliferation of the megalokaryocytes in Hodgkin's disease.

In leukemia, the picture in the marrow is very interesting. In typical cases (cases 21, 22 and 23), in treated or untreated patients, the pictures in the marrow and in the blood are similar. In aleukemic and subleukemic cases, study of the marrow should be of great diagnostic value (case 24).

Many problems for investigation are suggested by this study. A larger series of normal subjects and a greater number of patients with each pathologic condition should be studied. Infectious mononucleosis, essential granulopenia, malaria and other conditions remain to be investigated. Red cell counts, white cell counts and estimations of the hemoglobin content should be done on the oxalated marrow. The action on the marrow of various agents, such as nucleotides, adenine sulphate, roentgen rays, amidopyrine and benzene, may be studied. The material obtained by sternal puncture should be suitable for tissue culture.

CONCLUSIONS AND SUMMARY

1. A clinically practical method, modified from Arinkin, of obtaining bone marrow for biopsy by sternal puncture is described.

2. The simplicity of the technic and the accurate definition of cell morphology possible in the tissue so removed make this a valuable method for the study of the histogenesis of the blood cells and of the physiology of the bone marrow and for diagnosis.

3. The loss of structural relationships in marrow so removed is the only limitation of the method that does not apply to other methods of obtaining marrow from biopsy.

4. Differential, peroxidase and reticulocyte counts on the sternal marrow of twenty-eight healthy men and twenty-six patients with fifteen disorders of the hematopoietic system are reported and discussed.

5. Evidence was found that monocytes are derived from a stem cell (monoblast) similar in morphology to the myeloblast, that megalo-

24. Medlar, E. M.: An Interpretation of the Nature of Hodgkin's Disease, Am. J. Path. **8**:499 (Sept.) 1931.

blasts are precursors of normoblasts and are not the specific cell of pernicious anemia and that basophilic stippling occurs in the marrow.

6. Study of the sternal marrow established the diagnosis of aplastic anemia and subleukemic monocytic leukemia, and it aided in the differential diagnosis of Banti's disease from Gaucher's disease, of anemia of congenital syphilis from aplastic anemia and aleukemic leukemia and of multiple myeloma from a metastatic malignant process.

7. Other problems which may be solved by this method are suggested.

NOTE.—Since this article was written and the method was demonstrated at the Scientific Exhibit of the Eighty-fifth Annual Meeting of the American Medical Association in Cleveland, the method has been in regular use in a number of clinics, where its clinical practicability and diagnostic value have been demonstrated. We have studied the sternal marrow from over twenty-five additional patients. The method has proved especially valuable in the diagnosis of aleukemic myelosis and lymphadenosis. In malaria all stages of phagocytic digestion were observed in the bone marrow, a process which has not been observed to occur in the blood. A larger percentage of the erythrocytes in the marrow contained malaria parasites than of the erythrocytes in the blood, which was drawn at the same time. In infectious mononucleosis the typical large lymphocytes were demonstrated to be present in the marrow as well as in the blood.

EFFECT OF LIGHT MUSCULAR TRAINING ON PATIENTS WITH HEART DISEASE

RHEUMATIC HEART DISEASE; CHANGES AT REST AND DURING EXERCISE

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In recent years there have been numerous studies dealing with the effect of exercise on patients with heart disease. These studies have dealt almost exclusively with single acute experiments. While it is generally assumed that training increases one's capacity for work through the development of skeletal muscles, heart and lungs and better coordination of movements, so little is known about the effect of repeated exercises on patients with heart disease that there is a pronounced difference of opinion among cardiologists as to how harmful or beneficial such exercises are. The facts are few. The results of experiments with single exercises are not applicable. It was thought that by repeating a certain form of exercise over a period of several weeks, differences between people with normal hearts and those with diseased hearts, which were obscured in single exercises, might make themselves manifest. This refers only to patients with no evidence of failure of the right or left side of the heart and eliminates from consideration patients who are convalescing from heart failure.

The work of Oertel [1] and Schott,[2] which purports to demonstrate marked benefits from planned exercises, does not stand critical analysis. They judged improvement chiefly by subjective response on the part of the patient. Patients reported that they felt better, and they seemed to perform the more or less simple exercises with greater ease. Such evidence, while suggestive, is not conclusive. Among clinicians in general there are chiefly impressions, and these vary greatly, as to the rôle which exercise plays in patients with heart disease whose hearts are said to be "well compensated."

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From the Medical Clinic of the Boston Dispensary and the Department of Medicine, Tufts Medical School.

1. Oertel, M. J.: Die diatetisch-mechanische Behandlung der chronischen Herzmuskelerkrankungen, Vienna, Zeit- u. Streitfragen, 1889.

2. Schott, T.: Physikalische Behandlung der chronischen Herzkrankheiten, Berlin, Julius Springer, 1916.

For this study six patients with rheumatic heart disease were selected. They were between 18 and 22 years of age. Three of them had mitral stenosis and regurgitation with aortic insufficiency. The other three had only mitral stenosis and insufficiency. In one of the latter there was auricular fibrillation. The other five patients had normal rhythm. In one patient, a teleoroentgenogram showed only a bulge in the region of the left auricle. In the other patients, there was definite moderate enlargement of the heart both to the right and to the left. None of the patients showed evidence of failure of the right or left side of the heart. There was no sign of active infection. As controls, two people, aged 22 and 24, respectively, who had no evidence of heart disease and who were otherwise considered normal were studied.

Before and during the training period, usually from five to six weeks, frequent observations were made during rest under basal conditions on the following: pulse rate, respiratory rate, oxygen consumption, respiratory minute volume, cardiac output, velocity of blood flow, vital capacity, breath-holding ability, electrocardiograms and teleoroentgenograms. During exercise, changes were observed in pulse rate, respiratory rate, respiratory minute volume, blood pressure, oxygen consumption, velocity of blood flow, mechanical efficiency and lactic acid in the venous blood.

METHOD

The exercise was performed on a stationary bicycle designed by D. B. Dill of the department of biochemistry, Harvard University. It was of the Prony-brake type, with an automobile brake band and a cast-iron flywheel. The tension of the band on the drum was controlled by a screw adjustment which made it possible to keep the load constant in spite of changes due to the variations in friction. Such variations occurred especially at the beginning of exercise. The bicycle had a gear ratio of 1:2.2. A speedometer was attached to measure distance. During the first three days, before any exercise was begun, basal values were obtained. During the next three days, the patients pedaled on the bicycle for only ten minutes each day. Thereafter, all except the first two patients pedaled each day for one hour in the morning and one hour in the afternoon. The first two patients pedaled for six weeks, only one hour each day. Four of the patients continued the exercise for from four to six weeks; one for two weeks, another for fifteen weeks. Occasional short walks were also taken. The two patients who pedaled only one hour daily began their exercise by pedaling with each foot thirty times a minute (66 revolutions of the flywheel) against a pull of 2½ pounds (1,133.97 Gm.). This corresponded to 82.2 Kg. meters work per minute. The rate of pedaling was timed by a metronome. At the end of the first week of training the load was increased to 4 pounds (1,814.37 Gm.) at 66 revolutions per minute; the third week, 4 pounds (1,814.37 Gm.) at 88 revolutions and thereafter, 5 pounds (2,267.96 Gm.) at 115 revolutions per minute. The procedure was much the same for the other patients except that the pedaling was done for two hours daily, one hour in the forenoon and one hour in the afternoon; in the first two weeks with a pull of 4 pounds at 88 revolutions per minute; the third week, 5 pounds at 88 revolutions; the fourth week, 5 pounds at 95 revolutions, and the fifth week, 6 pounds (2,721.55 Gm.) at

115 revolutions, for two hours, and 6 pounds at 154 revolutions for ten minutes. The patient who trained for fifteen weeks pedaled, after the fifth week, for two hours daily against a pull of 6 pounds at 154 revolutions per minute.

Oxygen consumption was measured, using a 125 liter Tissot spirometer. Cardiac output was determined by means of the acetylene method of Grollman.[3] Sodium dehydrocholate (10 cc. ampules) was used as a means of measuring the circulation time from the cubital vein to the tongue.[4] Three injections of from 3 to 4 cc. each were given within three minutes. The measurements of the velocity of blood flow during exercise were made between the eighteenth and the twenty-first minute of exercise. The duration of the injection was between two and one-half and three seconds. The readings recorded are from the end of the injection. Subjective disturbances mentioned by Winkler[5] as likely to occur were not observed. Respiratory and pulse rates were obtained while the patients were breathing into the spirometer. The samples which were collected for gas analysis and estimation of oxygen consumption during exercise were always of the expired air for the three minutes between the seventh and tenth minutes of exercise. It was found, by measuring the oxygen consumption at various times during the hour of exercise, that in this period between the seventh and tenth minutes oxygen consumption had reached a steady state. During the heavier work, oxygen consumption was measured for only two minutes between the seventh and ninth minutes.

For studies of mechanical efficiency, oxygen consumption was measured between the twenty-seventh and thirtieth minutes, and the work was then increased by 1½ pounds (680.38 Gm.) while the subject was pedaling, everything else remaining unchanged. With the original work as the base line, the net efficiency was calculated from the excess oxygen required to pull the added 1½ pounds a measured distance. The heart rate was measured by counting for a full minute; the cardiac impulse, by palpation.

During the faster pedaling with greater work (a pull of 6 pounds at 152 revolutions per minute, 455 Kg. meters per minute), venous blood was taken between the ninth and tenth minutes during exercise for estimation of lactic acid. The method used for measuring the lactic acid was that of Friedemann, Cotonio and Shaffer.[6] The room temperature during the experimental procedure varied no more than 3 C. from day to day.

RESULTS

Changes at Rest: Pulse Rate, Respiratory Rate and Pulmonary Ventilation.—The pulse rate during rest under basal conditions on three successive days before training was between 55 and 60 per minute in the two normal persons. In the patients with heart disease the rate varied from 58 to 82, although in each patient it was practically the same on the three successive days. In all the patients the pulse rate

3. Grollman, A.: Determination of the Cardiac Output of Man by the Use of Acetylene, Am. J. Physiol. **88**:432, 1929.

4. Winternitz, M.; Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufszeit mittels Decholininjektion, Med. Klin. **27**:986, 1931.

5. Winkler, L.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufszeit mittels Decholininjektion, Med. Klin. **28**:83, 1932.

6. Friedmann, T. E.; Cotonio, M., and Shaffer, P. A.: Determination of Lactic Acid, J. Biol. Chem. **73**:335, 1927.

during rest, taken twice weekly, remained unchanged throughout the period of training.

In only one of the patients was the respiratory rate definitely changed. This was the patient (C. P.) in whom the most marked training effect [7] was observed. In this patient, the respiratory rate gradually decreased during the first month of training from 15 to 10 per minute. As in the other patients, there was no significant change in pulmonary ventilation.

Oxygen Consumption, Arteriovenous Oxygen Difference and Cardiac Output.—The oxygen consumption under basal conditions showed no essential change in any of the patients. Such results would be explained by Schneider and Foster [8] as due to a counterbalance between the new production of protoplasm and an increase in cellular efficiency: one tending to lower, the other to raise, the basal metabolic rate. The exercise, however, was hardly severe enough to make these factors of real significance.

TABLE 1.—*Changes in Cardiac Output During Training in a Patient with Rheumatic Mitral Stenosis and Insufficiency* *

Duration of Training	Oxygen Consumption, Cc. per Minute	Arteriovenous Oxygen Difference, Cc. per Liter	Cardiac Output, Liters per Minute
1 week	212	73.9	3.5
2 weeks	221	75.8	3.4
4 weeks (day before hemoptysis)	217	89.8	2.6
Following day (exercise stopped)	226	105.8	2.1
4 days later	212	67.2	3.1

* The exercise had to be discontinued because of the development of hemoptysis.

In one patient (T. McK.), the cardiac output showed an interesting change. After exhibiting practically no training effect, this patient began in the fourth week of training to experience discomfort while pedaling. Observations made during exercise showed a poor response to the work. The training was discontinued when he experienced a tightness across the chest and a cough with a slight hemoptysis while pedaling. In this case, the cardiac output per minute before training was 3.2 liters; after one week it was 3.5 liters, and after three weeks it was 3.4 liters. The day before the hemoptysis it was 2.5 liters; the day after, 2.1 liters. After four days, during which time the patient did not exercise, the cardiac output was 3.2 liters. The diminution in the cardiac output of this patient was associated with an increase in arteriovenous oxygen difference, as can be seen in table 1.

7. Here, as elsewhere, "training effect" is meant to indicate an improvement in response to exercise.

8. Schneider, E. C., and Foster, A. O.: Influence of Physical Training on the Basal Metabolism Rate of Man, Am. J. Physiol. **98**:595, 1931.

The cardiac output in the normal subjects, as well as in the patients with heart disease, was strikingly constant. In one of the normal persons, for example, the cardiac output per minute at rest and before training was 3.7 liters, with the arteriovenous oxygen difference, 57.4 cc. per liter and the oxygen consumption, 210 cc. per minute. At the end of training the cardiac output was 3.5 liters, with the arteriovenous oxygen difference, 57.5 cc. per liter and the oxygen consumption, 204 cc. per minute. In one of the patients with mitral stenosis the cardiac

TABLE 2.—*Velocity of Blood Flow at Rest (from Cubital Vein to Taste Buds of Tongue)*

Name	Diagnosis	Before Training, Seconds			During Training, Seconds					
					1st Week	2d Week	3d Week	4th Week	5th Week	6th Week
C. P.	Mitral stenosis;	16	14	15½	15	16	17	17	..	18½
	aortic insufficiency;		14		17	16	19	18	16½	
	normal rhythm		13		16	18	17	17	19½	17½
	Average	16	14	15½	16	17	18	17	18	18
P. B.	Mitral stenosis;	13	12	13	15	19	19	22	20	
	aortic insufficiency;	15	13	15	16	20	21	20	22	
	normal rhythm	14	12	14	18	21	20		22	
	Average	14	12	14	16	20	20	21	22	
J. L.	Mitral stenosis;	14	17	15	17	17	17	17	19	22
	aortic insufficiency;			17	18				22½	24
	normal rhythm	17		17	18½					
	Average	16	17	17	18	17	17	17	21	23
B. B.	Mitral stenosis;	..	..	24½	25½	24				
	auricular fibrillation				29	27				
				28½	27½					
	Average	..	..	27	27	26				
R. V.	Normal	17		16	16	18	11½	13½	16	
		13½		15	16	15	15½	16		
				17	17	16	15			
	Average	15		16	16	16	14	15	16	

output, taken repeatedly before and during the five weeks of training, varied only from 3.5 to 3.7 liters. The variations in the cardiac output in the other patients were only slightly greater and showed no definite rise or fall during the period of training.

Velocity of Blood Flow.—The speed of circulation, as measured by the sodium dehydrocholate method during rest, was within normal limits in all the patients except the one with auricular fibrillation. In this case, contrary to what was reported by Winternitz, Deutsch and Brüll,[4] the time of circulation was definitely prolonged (table 2).

The sodium dehydrocholate method for the measurement of the velocity of blood flow was generally satisfactory. However, the measure-

ments taken at rest were definitely less reliable than those taken during work. There was a sharper and more distinct taste during exercise than at rest, and the three measurements taken with each ampule of the sodium dehydrocholate checked more closely in exercise. Perhaps this is to be accounted for on the basis of a more rapid flow during exercise. However, in four of the patients and one of the normal subjects satisfactory results were obtained. The results in these cases are presented in table 2. A definite general training effect during exercise was observed in the three patients with regular rhythm. In these patients there was a slowing of the velocity of blood flow at rest. In the normal subject and in the patient with auricular fibrillation the general improvement during exercise was only slight. In these two subjects, no definite change in the velocity of blood flow at rest was observed. In the patient with auricular fibrillation, the exercise was continued for only two weeks.

Vital Capacity and Breath Holding.—Vital capacity and breath holding are considered together, although they are not necessarily tests of the same significance. It is our impression that measurement of the vital capacity is a greater aid in the study of cardiac function than is the estimation of the length of time the breath can be held. Breath-holding ability has certain variables which are not always easily controlled.[9] The subjective response to the stimulus for breathing may conceivably vary with practice. Also to be considered is the fact that many patients learn more or less subconsciously to breathe deeply a few times before they hold their breath. In this way the initial alveolar carbon dioxide content is lowered, and the patient is enabled to hold his breath longer. However, if satisfactory precautions are taken, breath holding may be of some value as an index of cardiac function, probably chiefly because of its relationship to the vital capacity of the lungs.

In the two normal subjects, the vital capacity remained unchanged during the period of training. The results in one of these are presented in figure 1. In two of the patients, however, slight but definite increase in the vital capacity was observed during the training period. In these two patients, a definite improvement in response to exercise was observed during the period of training. The single readings for vital capacity represent in each instance the maximum of three readings. The breath holding in these fairly well controlled cases was observed generally to parallel the vital capacity.

9. Palcso, B.: Der Wert der Zeitdauer des Atemhaltenkönnens in der funktionellen Herzdiagnostik, Ztschr. f. Kreislaufforsch. **20**:457, 1928. Katz, L. N.; Hamburger, W. W., and Rubinfeld, S. H.: Observations on the Effect of Oxygen Therapy: Changes in the Circulation and Respiration, Am. J. M. Sc. **184**:810, 1932.

Electrocardiograms.—In one of the patients, no change was observed in the electrocardiogram. This was one of the two patients with involvement of only the mitral valve who showed no training effect during exercise. In the three patients who showed a definite effect, the following changes were noted: in one, a slight increase in the height of the P wave in lead II, and in the others (J. L. and C. P.) an increase in the height of the T waves, as shown in the electrocardiogram. In the patient who had a slight hemoptysis there was, following the hemoptysis, an increase in the P R interval from 0.16 to 0.18 second, and although the axis of the QRS wave remained unchanged, the P waves changed, P_2 becoming less prominent and P_3 wholly inverted,

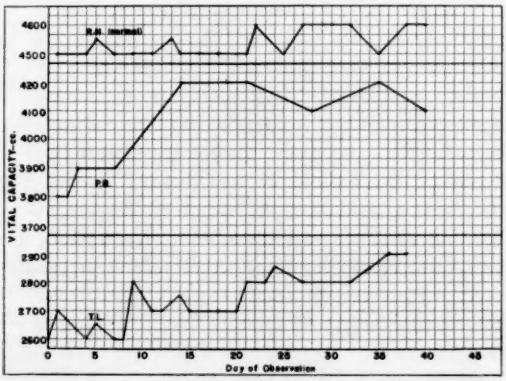

Fig. 1.—Changes in vital capacity occurring in one normal subject and in two patients with mitral and aortic valvular disease. The days indicate the period of training.

as shown in the electrocardiogram. We are unable to explain the significance of this change.

Teleoroentgenograms.—Teleoroentgenograms were taken on three successive days before exercise was begun; one was taken weekly throughout the period of training, and three were again made at the end of training. Small variations in cardiac measurements were seen in the three teleoroentgenograms before exercise was begun, probably owing to slight changes in position, the period of respiration, etc. Changes greater than what might be considered normal variations did not occur during the period of training. While the exercise was perhaps not severe enough or of sufficient duration to cause changes in the size of the heart, it seemed to us that slight changes might occur, especially in the size of the left auricle in the case of mitral stenosis. Careful measurements, however, failed to reveal such changes.

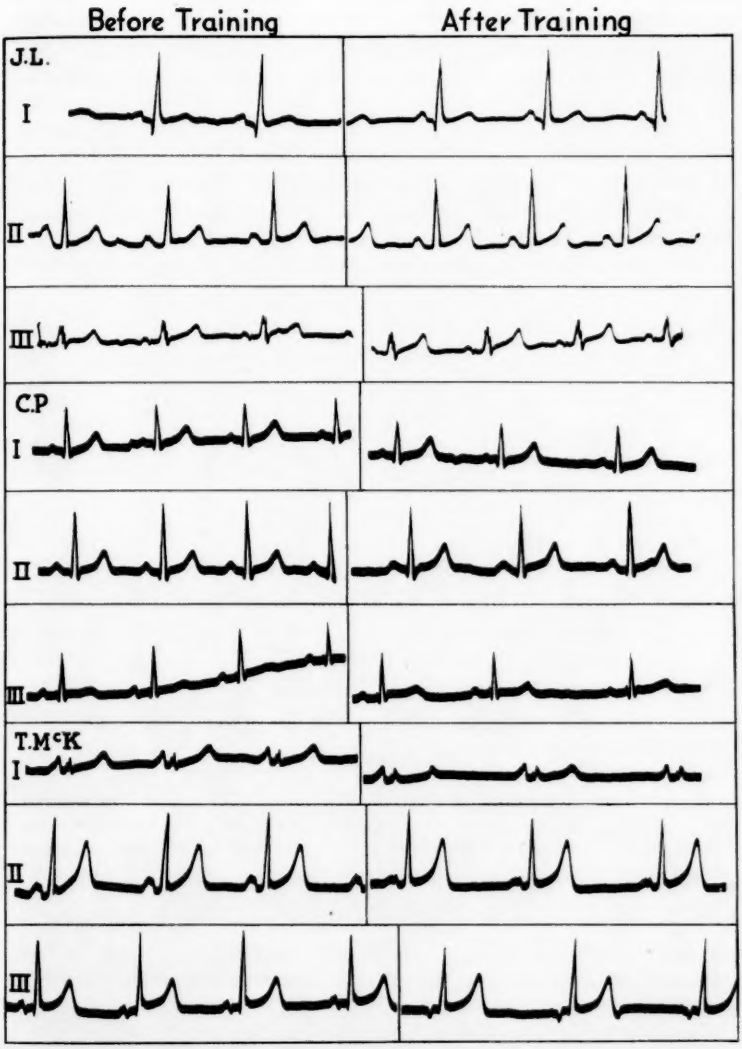

Fig. 2.—Electrocardiograms taken before and after training, showing, in the cases of J. L. and C. P., an increase in the height of the T waves and in the case of T. McK. a slight increase in the P R interval, lowering of P_2 and inversion of P_3.

CHANGES DURING EXERCISE

In general, it may be said that in the two normal people there was a slight training effect; in the three patients with disease of both aortic and mitral valves, a definite and rather marked training effect; in the two patients with only mitral disease and with regular rhythm, no training effect, and in the one patient with mitral stenosis and auricular fibrillation, a slight effect. In one of the two patients with mitral stenosis and regular rhythm, the training had to be discontinued during the fourth week because of the development of a feeling of tightness across the chest and a slight hemoptysis. The various types of response are recorded in the charts.

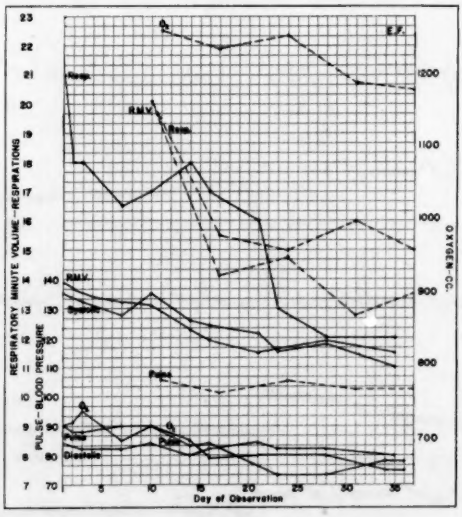

Fig 3.—Changes occurring during exercise in a normal subject. In the first three days the exercise consisted of pedaling on a stationary bicycle for ten minutes daily, thereafter for one hour twice daily. The dotted lines represent changes during heavier work and the solid lines, changes during moderate work.

Figure 3 represents the changes which occurred in one of the normal persons. The other normal person did not differ essentially in his response. There was a slight training effect, an effect of about the magnitude which might be expected in a normal person with the exercise which we studied. Within the first three weeks, the oxygen consumption for the lighter work dropped from 720 to 680 cc. per minute, the respiratory minute volume, from 13.85 to 11.5 liters, the blood pressure, from 136 systolic and 84 diastolic to 110 systolic and 80 diastolic, the pulse rate, from 90 to 74 per minute and the respiratory rate, from 21 to 13 per

minute. There were corresponding changes during the heavier work. These results in a normal person correspond to those reported by Gemmill, Booth and Pocock.[10]

Figure 4 represents the most striking training effect which we observed. The patient had mitral stenosis and insufficiency and aortic

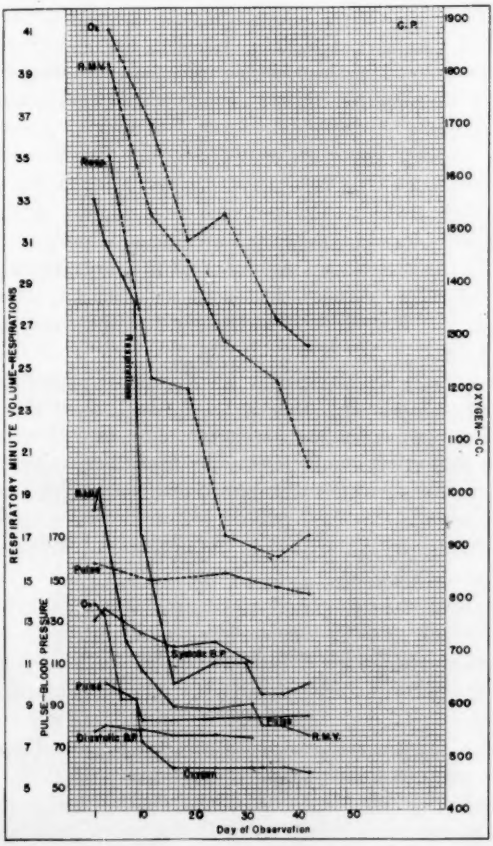

Fig. 4.—Changes occurring during exercise in a patient with rheumatic mitral and aortic valvular disease. During the first three days of observation pedaling on a stationary bicycle was carried out for ten minutes daily, and thereafter for one hour daily. The dotted lines represent changes during heavier work and the solid lines, changes during moderate work.

10. Gemmill, C.; Booth, W., and Pocock, B.: Muscular Training: Physiologic Effect of Daily Repetition of Same Amount of Light Muscular Work, Am. J. Physiol. **92**:253, 1930.

insufficiency, moderate cardiac enlargement to both the right and the left and definite enlargement of the left auricle. It is noted that there was a marked change in the cardiovascular response to the same exercise as the training was continued to the forty-second day. The changes during the first three days must be taken to be due chiefly to overcoming excitement and awkwardness, inevitably associated with the exercises at the beginning. (On these days the patients rode for only ten minutes.) Beyond these first few days, however, the changes must be due to adjustments in the cardiovascular apparatus and lungs. It might be noted here that this patient was a very calm, husky, athletic youth who had been living a fairly active life (swimming, playing handball and hiking) just before our studies were begun. Most of the improvement in performing the light work had taken place at the end of sixteen days. Thereafter, the changes were only slight. In these sixteen days, the oxygen consumption per minute during exercise dropped from 790 to 480 cc., the respiratory rate from 33 to 10 per minute, the pulse rate from 100 to 82 per minute, the blood pressure from 130 systolic and 78 diastolic to 110 systolic and 74 diastolic and the respiratory minute volume from 18.25 to 8.9 liters. In the heavier exercise (represented by the dotted lines) the changes were of similar magnitude; only the pulse rate changed relatively less, from 158 to 142 per minute. However, since 158 approaches the maximum pulse rate obtainable during exercise, it is likely that this initial rapid pulse rate represents a restricted level, owing to the factors which limit increasing pulse rate beyond a certain level, whereas the final rate of 142 represents a straight rise to that figure. Thus, real differences in the response of the pulse rate may be obscured at such levels.

Figure 5 shows the changes which occurred in the patient with mitral stenosis and insufficiency in whom the exercise had to be discontinued because of the development of hemoptysis. There was relatively little change during the early stage of training. After the fourth day, which in this instance corresponded to the day when training was begun, to the twenty-seventh day, the pulse rate, systolic and diastolic blood pressures and oxygen consumption remained practically constant. After the twenty-seventh day they rose gradually, indicating a less efficient response to the exercise, until the training was discontinued on the thirty-second day because of hemoptysis. The failure of this patient to improve with exercise is as definite as the marked improvement in the previous patient presented. Another patient with only mitral disease also showed no improvement with exercise, although he did not give evidence of being any the worse for the exercise.

Figure 6 shows the changes which took place over a period of fifteen weeks in a patient with aortic and mitral valvular disease. For the

first twenty-two days there was a distinct improvement in the circulatory and respiratory response to exercise. Then for a few days the reverse effect took place, the pulse rate, oxygen consumption, respiratory rate, etc., increasing, although the work remained the same. After a few days this paradoxical change disappeared, and the previous level of

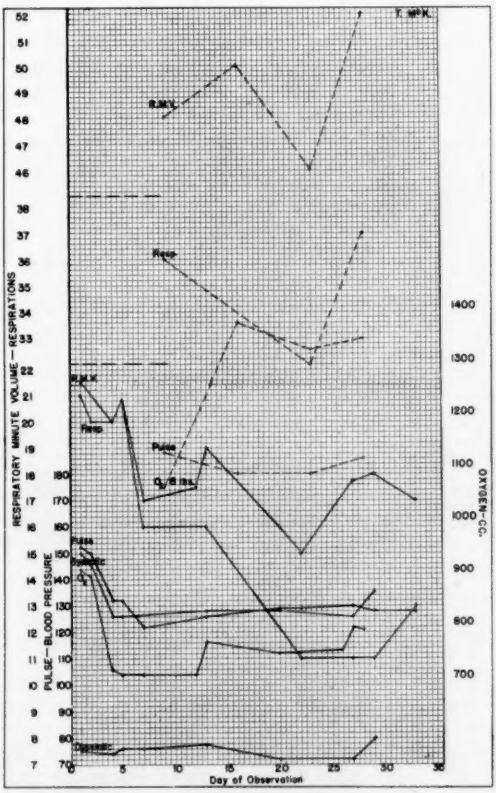

Fig. 5.—Changes occurring during exercise in a patient with rheumatic mitral disease. In the first four days the exercise was for ten minutes daily, and thereafter for one hour twice daily. On the thirty-second day exercise was discontinued because of the development of hemoptysis. The dotted lines represent changes during heavier work and the solid lines, changes during moderate work.

response was reached and maintained thereafter. This loss, as it were, of training effect for several days was demonstrated by the results of several experimental periods, so that the change cannot be attributed to an experimental error. During this period there was no evidence of

undue excitement or tension on the part of the patient. In the evening of the eighty-sixth day of exercise, this patient showed a moderately severe pharyngitis with a temperature of 101 F. He remained in bed for two and one-half days, during which time the exercise was discontinued. When exercise was resumed on the ninetieth day, there was no indication that the infection had impaired his response to exercise.

Velocity of Blood Flow.—In figure 7 are shown the changes in the velocity of blood flow during exercise in the course of training in the three patients who had a distinct training effect and in one normal subject. In the normal subject, the velocity was slowed from ten and a

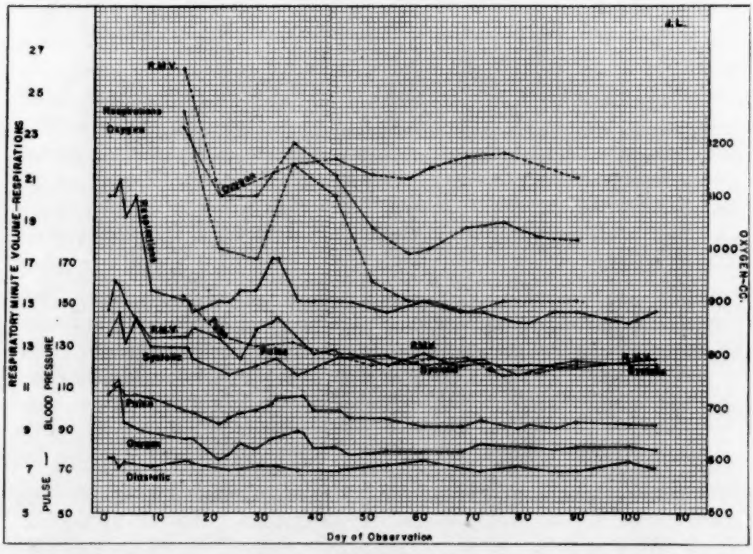

Fig. 6.—Changes occurring during exercise in a patient with rheumatic and aortic mitral disease. In the first three days the exercise was for ten minutes daily, and thereafter for one hour twice daily. The dotted lines represent changes during heavier work and the solid lines, changes during moderate work.

half to sixteen and a half seconds. In the patients there was also a distinct slowing of from three to four seconds over a period of from four to five weeks. As noted previously, the sodium dehydrocholate method proved especially satisfactory during exercise, the results of three successive injections within a few minutes rarely varying more than one second. For example, in the case of P. B. the following results were obtained on the six occasions when the velocity of blood flow was measured during exercise: (1) ten seconds, (2) ten, nine and one-half and ten seconds, (3) ten and one-half, eleven and eleven seconds, (4)

eleven and one-half, eleven and one-half and eleven and one-half seconds, (5) twelve, thirteen and thirteen seconds and (6) thirteen and one-half, fourteen and thirteen and one-half seconds. In the patient with auricular fibrillation, the velocity of blood flow during exercise and at rest was unusually slow. During the three weeks in which this

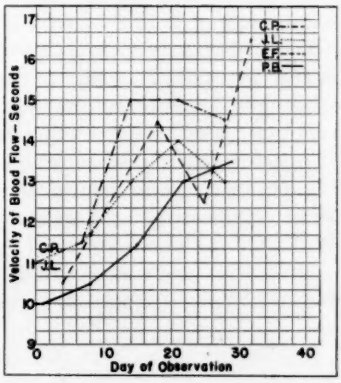

Fig. 7.—Velocity of blood flow in exercise.

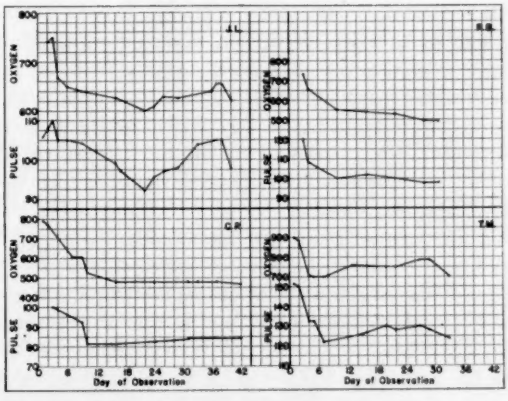

Fig. 8.—Changes in the pulse rate and consumption of oxygen during exercise in four patients. Note the striking parallelism.

patient trained, the time of circulation from the cubital vein to the taste buds of the tongue remained between twenty-one and twenty-three seconds. During this time only a slight general improvement in cardio-respiratory response was noted, as measured by the other tests of this study. In the two patients who showed no improvement in exercise,

the velocity of blood flow during exercise remained unchanged throughout the period of training, the difference in one patient being one second, and in the other patient two seconds, between the first and last estimations.

Pulse Rate.—An interesting observation is recorded in figure 8. It may be noted that there was a striking parallelism between the pulse rate and the oxygen consumption during exercise throughout the period of training. As the pulse rate became slower during the same exercise, the oxygen consumption dropped. Usually we were able to predict, from a change in pulse rate, a change in oxygen consumption. The pulse rate was found not to be as effective an index of mechanical efficiency when it was measured simply in the resting state, or even when the length of time required for it to return to a resting state after exercise was measured. These two measurements were found to be distinctly more variable than the measurement of the pulse rate during exercise. Uncontrolled and not easily explained spontaneous variations occurred in the former instances, whereas they were relatively rare in the latter.

Since the pulse rate during exercise seemed to be such a reliable index of the oxygen consumption in the same person, we should expect the pulse rate to remain at a constant level during the exercise, just as the level of oxygen consumption remained fixed, the patient being in a "steady state." It was found that the pulse rate was, in fact, constant during the hour of exercise. However, Bowen [11] reported that there is, at the beginning of exercise, a sudden increase in pulse rate followed by a more gradual secondary rise, continuing to the end. Gillespie, Gibson and Murray [12] agreed with Bowen, but added that the pulse rate gradually increases "except possibly during the lightest work." Gillespie, Gibson and Murray also found that because of the tendency of the pulse rate to rise during exercise, the influence of successive increments of load on the pulse was not clearly distinguishable. Under the conditions of our experiment, however, successive increments of load, even relatively slight, were accompanied by a distinct increase in pulse rate. Thus, in table 3, it is seen that the pulse rate at an oxygen consumption of about 780 cc. was constant during the hour. In another experimental period with the rate of pedaling constant and the load increased from 4 to 5½ pounds (1,814.31 to 2,494.75 Gm.), the pulse rate increased from 93 to 102, corresponding in this case to an increase in oxygen consumption from 620 to 740 cc. per minute. The pulse rate then decreased from 102 to 94 per minute when the load was decreased from

11. Bowen, W. P.: Changes in Heart Rate, Blood Pressure and Duration of Systole Resulting from Bicycling, Am. J. Physiol. **11**:59, 1904.

12. Gillespie, R. D.; Gibson, C. R., Jr., and Murray, D. S.: Effect of Exercise on Pulse Rate and Blood Pressure, Heart **12**:1, 1925.

5½ to 4 pounds. There was a corresponding fall in oxygen consumption from 740 to 615 cc. per minute.

The relationship of oxygen consumption to pulse rate in the same person was not the same when the differences in oxygen consumption were due to differences in load as when they were due to training effect. Thus, whereas a decrease of 125 cc. in oxygen consumption due to a decrease in load was accompanied by a decrease of 8 in pulse rate (J. L., table 3), a decrease of 140 cc. in oxygen consumption due to a training effect was accompanied by a proportionately greater decrease, 16, in the pulse rate (J. L., fig. 8). The oxygen consumption in the two instances was in the same general range.

Mechanical Efficiency.—The changes in net mechanical efficiency corresponded grossly to the changes in oxygen consumption during work, as shown in the various figures. Thus, in the case of C. P. (fig. 4), there was an increase in net efficiency from 14.9 to 26.6 per cent. In the normal subject, in whom the decrease in oxygen consumption during work was considerably less (fig. 1), the increase in net efficiency was from 22.6 to 26 per cent.

TABLE 3.—*Vital Capacity in the Course of Training in Two Patients with Rheumatic Mitral Stenosis and Aortic Insufficiency, and One Normal Subject*

Date	Time of Exercise, Minutes	Pulse Rate per Minute	Oxygen Consumption, Cc. per Minute	Work, Kg. Meters per Minute
1/12/33	7-10	112	770	255
	27-30	111	785	255
	57-60	111	785	255
3/ 3/33	7-10	93	620	175
	11	...	...	240
	19-22	102	740	240
	23	...	...	175
	31-34	94	615	175

Lactic Acid.—In one normal subject (E. F., fig. 3) and one patient (J. L., fig. 6) venous blood was taken in the ninth minute of the heavier exercise for the estimation of lactic acid. In the normal subject, the lactic acid content gradually decreased with training from 39 to 28 mg. per hundred cubic centimeters. In the patient with rheumatic mitral and aortic disease, the lactic acid content of the blood during the exercise gradually decreased over a period of nine weeks from 38 to 13 mg. The last figure represents practically the resting value, and indicates that after nine weeks a true "steady state" had been reached by this patient even for the heavier work (oxygen consumption, 1,100 to 1,200 cc). Bock, Dill and Edwards [13] found that work of this severity (moderate physical

13. Bock, A. V.; Dill, D. B., and Edwards, H. T.: Lactic Acid in Blood of Resting Man, J. Clin. Investigation **11**:775, 1932.

exercise) for thirty minutes was accompanied by no increase in the lactic acid in the venous blood. In the light of their results, our findings are to be interpreted to indicate that in the tenth minute of the work in our normal subjects, removal or resynthesis of lactic acid was still not keeping pace with its production. In the case of the last patient referred to, however, after nine weeks of training, and at a time when the patient was training for two hours daily with the work under consideration, the lactic acid level had reached a resting level in the tenth minufe.

Blood Pressure.—In exercise of the severity which we were studying a definite elevation of blood pressure occurs usually only in the systolic phase.[14] Therefore, it is to be expected that the lowering of the blood pressure during exercise which takes place in the course of training should be a lowering, essentially, of the systolic pressure. This is clearly shown in figure 4 (C. P.). The blood pressure at the beginning of training was 130 systolic and 78 diastolic during exercise; at the end of thirty-one days it was 110 systolic and 74 diastolic during exercise. There was a drop in systolic pressure of 20 mm. of mercury, while the diastolic pressure remained practically unchanged. Similar changes occurred in the other patients who showed a good response to training. In patients who showed no training effect, no significant changes were observed in either systolic or diastolic blood pressure.

COMMENT

In determining the significance of the changes observed in the resting state during a period of training, especially in dealing with patients with heart disease, it is important to know whether the patient during the period of observation is engaging in more or less activity than usual. Since the patients were in a ward during a large part of the day, their total activity was not great. However, the total physical activity of only two of the patients was less than usual while they were under observation. The activity of the other four patients was severely limited before we began our studies, more through fear and overcautiousness on their part than because of extreme restriction on the part of their physicians. In these two groups, the previous mode of life seemed not to play as important a rôle as might be expected. Of course, none of the patients was previously trained to ride a bicycle, so that regardless of the state of physical development and previous exercise a new type of work was being performed by all of them, and groups of muscles

14. (*a*) Bock, A. V.; Vancaulaert, C.; Dill, D .B.; Fölling, A., and Hurxthal, L. M.: Studies in Muscular Activity: III. Dynamic Changes Occurring in Men at Work, J. Physiol. **66**:136, 1928. (*b*) Bansi, H. W., and Groscourth, G.: Funktionsprüfung des Kreislaufs durch Messung der Herzarbeit, Klin. Wchnschr. **9**:1902, 1930. (*c*) Proger, S. H., and Dennig, H.: A Study of the Circulation in Obesity, J. Clin. Investigation **11**:789, 1932.

were used in a manner hitherto not employed in daily activities. Hyde, Root and Curl [15] showed that the training effect observed in trained and untrained subjects is not essentially different when each performs a work to which he is not accustomed; in their study, pulling on an ergometer. In any event, the changes reported in the resting state may be taken as changes which occur in patients with rheumatic heart disease during a period of several weeks of moderate physical activity.

The changes in cardiac output which occurred in the one patient who responded so poorly to exercise are of interest. It will be recalled that the drop in cardiac output, associated with hemoptysis and diminished vital capacity, took place largely through an increase in the arteriovenous oxygen difference. It has been suggested before that one of the reserve mechanisms which the cardiovascular apparatus employs when the heart itself tends to become incompetent is an increase in the arteriovenous oxygen difference.[16] This is borne out by the fact that the cardiac output at rest in patients with varying degrees of heart failure is relatively low,[17] while the oxygen consumption or basal metabolism, except in patients with advanced heart failure, is practically unchanged.[18] The change in cardiac output is associated with an increase in oxygen utilization in the tissues, with a subsequent increase in the arteriovenous oxygen difference.

In the patient referred to, it is conceivable that because of pulmonary congestion there was a considerable increase in the length of time necessary for rebreathing, in order to obtain a true alveolar sample. In such a case, a high incorrect figure would be obtained for the arteriovenous oxygen difference, since the samples were taken at the usual times (eighteen and twenty-three seconds). The objection might also be made that the pulmonary congestion might even make it impossible to obtain true alveolar air samples. However, on the basis of the work of Grollman, Proger and Dennig,[19] the degree of pulmonary congestion in this case was not so great as to make such objections tenable.

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15. Hyde, I. H.; Root, C. B., and Curl, H.: A Comparison of the Effects of Breakfast, of no Breakfast and of Caffeine on Work in an Athlete and a Non-Athlete, Am. J. Physiol. **43**:371, 1917.

16. Dennig, H., and Proger, S. H.: Herzkranke bei Arbeit, Deutsches Arch. f. klin. Med. **175**:170, 1933.

17. Kroetz, C.: Messung des Kreislaufminutenvolumens mit Acetylen als Fremdgas: Ihre bisherigen Ergebnisse bei arteriellem Hochdruck und bei Dekompensation des Kreislauf, Klin. Wchnschr. **9**:966, 1930.

18. Du Bois, E. F.: Basal Metabolism in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1927, p. 364.

19. Grollman, A.; Proger, S. H., and Dennig, H.: Zur Bestimmung des Minutenvolumens mit der Azetylenmethode bei Arbeit, bei normalen und kranken Menschen, Arch. f. exper. Path. u. Pharmakol. **162**:463, 1931.

In the normal persons no change was observed in the vital capacity. There is very little convincing evidence that training involving even severe exercise affects considerably the vital capacity in the normal person.[20] It is the impression of some [21] that training does increase the vital capacity of normal persons, since trained athletes frequently have a greater vital capacity than nonathletes. Such evidence is only indirect, and it is open to the criticism that greater vital capacity, among other things, may be an inherent property of a person which enables him to develop into a first class athlete, whereas the person with a lower vital capacity never becomes an athlete. The increase in vital capacity which was observed in some of the patients during the training is striking evidence that some real form of cardiovascular adjustment takes place, perhaps in much the same manner as when heart failure without clear evidence of pulmonary congestion is being overcome when marked increase in vital capacity is seen. These changes indicate also that in the patient with heart disease, even when there is no evidence of cardiac weakness, the vital capacity may be somewhat less than it would be under normal conditions. Just why only two of the patients who showed a definite improvement in ability to perform the work had an increase in vital capacity, while the others did not, we are unable to say.

In the evaluation of the results of training, it becomes necessary to attempt to determine how much, if any, of the change during exercise is due to actual changes within the skeletal muscles, heart and lungs, and how much is due simply to a better coordination of movements as the result of practice. Because the work is light, one might be inclined to assume that the changes are the result chiefly of a neuromuscular adjustment, and that the development of a more efficient response to work is the result simply of less awkwardness in its performance. Had the normal subjects and the patients with heart disease responded alike to the long repeated exercises, such a view would be justifiable. It is even probable that the slight changes observed in the normal subjects were due wholly to the development of better coordination of movements. But the changes which were observed, for example in the patient of figure 4, are of such magnitude as to imply some real changes within the cardiovascular apparatus itself. Just what these changes are it is difficult to

20. White, S. A., and McGuire, P. F.: Vital Capacity in a Citizens Military Training Camp, Arch. Int. Med. **36**:355 (Sept.) 1925. Wachholder, K.: Die Vitalkapazität als Mass der körperlichen Leistungsfähigkeit, Klin. Wchnschr. **7**: 295, 1928.

21. Worringen: Ztschr. f. d. ges. phys. Therap. **31**:132, 1926. Godin, P.: Contrôle de l'éducation physique; la croissance pendant l'âge scolaire, Paris, Norbert Maloine, 1913, p. 205. Bainbridge, F. A.: The Physiology of Muscular Exercise, ed. 3, rewritten by A. V. Bock and D. B. Dill, New York, Longmans, Green & Co., 1931, p. 182.

determine. Probably one significant change is the increase in the vital capacity of the lungs which was observed. The fact that there were such marked differences in responses in a group of similar patients would make it seem also that something more than a neuromuscular adjustment was involved. Also, because for many days after training was begun, when there was no longer awkwardness in the performance of work or anxiety, significant changes continued to occur, one would be inclined to believe that actual physicochemical changes within the heart and skeletal muscles were taking place.

Gemmill, Booth and Pocock [10] concluded from their study of three normal persons that training to light muscular work brings about an increase in the efficiency of the cardiac and respiratory mechanisms rather than a change in the efficiency of the muscles. Such a change might be brought about, they thought, by changes in the oxidative mechanism of the cells, as suggested by Hill and Lupton [22] and Bock and his associates,[14a] by an increase in the effective surface of the capillary bed supplying the muscles, or by changes in the nervous control of respiration and circulation during work.

The reason for the differences in response to training in the various patients is not clear. On the basis of the information at hand, it is not possible to predict what type of patient would and what type of patient would not show improvement with light exercise. That some do and some do not is obvious from the results. Perhaps it is significant that of the five patients studied who had regular rhythm, the three who showed a distinctly good training effect had disease of both the mitral and the aortic valves, whereas the two patients who showed no training effect (one of these had to stop the exercise because of a hemoptysis) had disease of the mitral valve alone. It might be thought that the changes which occur during training, whatever they are, are dependent on an adjustment between the greater and lesser circulations which can take place in the patient with a balanced disturbance, as it were, in both valves, whereas it cannot take place in a patient with the imbalance resulting from disease only of the mitral valve. This is simply a theoretical assumption and perhaps unjustified because of the small number of patients which we have studied, but it is consistent with the clinical observation that patients with mitral disease alone sometimes seem better when aortic insufficiency develops in addition.

One phase of the results in the patient the observations on whom are represented in figure 6 deserves special comment. We refer to the general increase in the values, which began after a distinct training effect had already occurred, that is, on the twenty-second day. There was an

22. Hill, A. V., and Lupton, H.: Muscular Exercise, Lactic Acid and Supply and Utilization of Oxygen, Quart. J. Med. **16**:135, 1923.

unexplained loss of efficiency over a period of several days, during which time repeated observations were being made. There was, during this period, no evidence of infection, rheumatic or otherwise, nor were there subjective changes. Before this stage, the patient had obviously already reached what appeared to be the "trained" state for that particular exercise, so that the changes cannot be associated with possible differences in muscular coordination or skill in the performance of the work. There was no reason for the patient to become more awkward. It was thought that perhaps this phase represented very early evidence of heart failure, although the usual factors ordinarily associated with early failure of either the left or the right side of the heart were not manifested. Thus, there were no increasing shortness of breath, no tachycardia, no diminished vital capacity or breath-holding capacity, no cough and no increase in the intensity of the second sound over the pulmonic area. However, the increasing inefficiency was definite, although after a few days there was a return to the level of the "trained" state. Because of the possibility that early heart failure might occur in steplike fashion in a manner somewhat similar to late heart failure when there is usually more than one "break in compensation" before the end, exercise was continued for about eighty days after this unusual phase. A similar decrease in efficiency was not noted. The earlier reaction remains simply an interesting but unexplained phenomenon.

As early as 1915, Boothby [23] observed that "in the main, the pulse rate increases with oxygen consumption" in the human being. The results in these patients indicate that not only does the pulse rate vary directly with varying consumption of oxygen associated with different grades of work, but that the parallelism exists also when the consumption changes with the same work as in training. Because of this fact, the pulse rate during exercise served as a fairly accurate index of the mechanical efficiency. As the mechanical efficiency increased, the pulse rate during exercise became lower, and vice versa. Excitement was, of course, not present as a disturbing factor because of the continued repetition of the periods of exercise. As a result of these observations, it appears that measuring the pulse rate during exercise in patients with heart disease may serve as a helpful functional test. Assuming that the gross mechanical efficiency diminished with increasing cardiac weakness, we should expect to be able to detect such a state in a single person if his pulse rate were measured during the same exercise on different days. While differences in pulse rates in different persons are of no value, differences occurring in the same person would seem to be of real value as a guide to the physical state of a patient, and thus, perhaps, to the

23. Boothby, W. M.: A Determination of the Circulation Rate in Man at Rest and at Work, Am. J. Physiol. **37**:383, 1915.

functional state of his cardiovascular apparatus. This does not apply to all types of heart disease, for observations which we have made on some patients with angina pectoris, even of the advanced type, indicate that frequently the pulse rate responds unusually slowly to exercise in this condition.[24]

The pulse rate during exercise was found to be considerably more constant than the rate either at rest or after exercise. Spontaneous unexplained fluctuations not infrequently occurred under the latter circumstances. The length of time necessary for the pulse rate, after exercise, to return to the resting level was also not constant enough in our experiments to be of great aid as a guide to the efficiency with which the work was performed.

SUMMARY

1. Six patients with rheumatic heart disease pedaled on a stationary bicycle for from one to two hours daily for a period of from five to six weeks. Two normal persons in the same age group served as controls.

2. There were essentially no changes at rest in the pulse rate, respiratory rate (except for slowing in one case), pulmonary ventilation and oxygen consumption.

3. In one patient in whom exercise had to be discontinued because of the development of hemoptysis, the arteriovenous oxygen difference at rest showed an increase, and the cardiac output a decrease, just before and after the hemoptysis. These values returned to normal within a few days after the exercise was discontinued. In the other patients, the arteriovenous oxygen difference and cardiac output at rest were unchanged.

4. In the patients who improved with exercise, there was a slight slowing of the velocity of blood flow at rest.

5. The vital capacity in two of the patients who improved with exercise showed a definite increase. In the normal subjects, as well as in the other patients, it remained unchanged. Breath-holding ability generally paralleled the vital capacity.

6. Of the three patients who showed definite improvement in their response to exercise, there was an increase in the height of P_2 in the electrocardiogram in one, and in the others an increase in the height of the T waves. In the patient in whom hemoptysis developed there was a slight prolongation of the P R interval, an increase in the height of P_2 and an inversion of P_3.

7. There were no definite changes in the teleoroentgenograms.

24. Proger, S. H.; Minnich, W. R., and Magendantz, H.: Circulatory Response to Exercise in Patients with Angina Pectoris, Am. Heart J., to be published.

8. As determined by observations during exercise, the two normal subjects showed slight improvement; three patients with disease of both aortic and mitral valves showed marked improvement; one patient with only mitral disease showed no change, while another grew worse, and the only patient with an irregular heart beat (auricular fibrillation) who also had mitral stenosis and insufficiency showed a very slight improvement.

9. A possible explanation for the varying responses is suggested.

10. In one patient, after improvement had taken place, an unexplained relapse occurred which was overcome in a few days. In the same patient a mild infection with fever caused no change in his response to exercise immediately before and after the febrile state.

11. A striking parallelism is shown to exist between the pulse rate and oxygen consumption during exercise through the period of training.

COPPER AND IRON IN HUMAN BLOOD

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I NORMAL MEN AND WOMEN

The biologic importance of copper was brought to light by Bucholz and Meissner [1] in 1816, when they identified this element in plant life. Deverzie and Orfila,[2] in 1840, described the presence of copper in animal tissue. It was later recognized that all plant and animal tissue contains traces of copper. However, these traces were believed to be accidental, and no definite function was assigned to the element. Toward the latter part of the nineteenth century, copper was found in the blood of some marine animals.[3] Porter [4] reported appreciable amounts of copper in human blood in 1875.

BIOLOGIC FUNCTIONS OF COPPER

The function of copper in the biologic organism has, as a result of recent experimentation, become more clearly defined. Copper acts chiefly as a catalyst with reference to (1) growth, (2) respiration and (3) hematopoiesis.

Growth.—The earliest function assigned to copper was that of a promoter of growth. This function was inferred from the fact that the element was found in greatest abundance in the most actively growing parts of plants.[5] Later experiments proved that copper was actually

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1. Bucholz, C. F., and Meissner, W., cited by Elvehjem, C. A., and Lindow, C. W.: The Determination of Copper in Biological Materials, J. Biol. Chem. **81**:435 (Feb.) 1929.

2. Deverzie and Orfila, cited by Herkel, W.: Ueber die Bedeutung des Kupfers in der Biologie und Pathologie, Beitr. z. path. Anat. u. z. allg. Path. **85**:513 (Nov.) 1930.

3. Church, A. M.: Researches on Turacin, an Animal Pigment Containing Copper, Phil. Tr. London **159**:627, 1869; continued, Proc. Roy. Soc. London **51**:399, 1892.

4. Porter, J. A.: Principles of Chemistry, improved edition, New York, Barnes, 1875, p. 333.

5. Maquenne, L., and Demmoussey, E.: Sur la distillation et la migration du cuivre dans les tissus des plantes vertes, Compt. rend. Acad. d. sc. **170**:87, 1920.

able to increase the growth of plants.[6] Too concentrated a dose, however, inhibited growth. The presence of copper in instances of rapid growth has been confirmed for animals also. Rats maintained on a diet rich in copper showed a greater increase in weight than litter mates maintained on a diet restricted in copper.[7] In almost all lower animals the liver of the embryo and of the new-born contains a higher percentage of copper than for that of the adult of the same species.[8] In man the liver of the fetus also shows a higher percentage of copper than does the adult liver.[9] Such relative increase may represent the need for copper during the period of rapid growth. Most investigators prefer, however, to regard the excessive storage of copper and iron in the fetal liver as necessary to supplement the potential anemia-producing diet on which the infant is to subsist in the first year of extra-uterine life.

Respiration.—Copper plays an important rôle in the respiratory process of certain crustaceans and mollusks. In hematocyanine,[10] the respiratory pigment found in the colorless and blue blood of these marine animals, copper assumes the function that iron performs in the hemoglobin of warm-blooded animals. Aside from this outstanding instance of the ability of copper to act as a respiratory catalyst, the conclusions reached in other investigations on the relationship of copper to respiration are in a confused state. The confusion arises from a failure to distinguish the toxic property of copper from its stimulating or catalyzing ability. The beneficial influence of minute quantities of copper is rapidly converted into a malignant oligodynamic factor as the concentration in a given medium goes up. Although known to depress the respiration of yeasts and other lower forms, copper in physiologic concentration acts as a stimulant. Flinn and Inouye [7] found that copper increases the oxygen-combining capacity of the blood, while Guillemet [11] traced in animals a proportionality between the respiratory capacity and the copper content of the blood.

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6. Allison, R. N.; Bryan, O. C., and Hunter, J. H.: Florida Agric. Exper. Sta. Bull., 190, 1927.

7. Flinn, F. B., and Inouye, J. M.: Some Physiological Aspects of Copper in the Organism, J. Biol. Chem. **84**:101 (Oct.) 1929.

8. Cunningham, I. J.: Some Biochemical and Physiological Aspects of Copper in Animal Nutrition, Biochem. J. **25**:1267, 1931.

9. Morrison, D. B., and Nash, T. P., Jr.: The Copper Content of Infant Livers, J. Biol. Chem. **88**:479 (Sept.) 1930.

10. Fredericq, L.: Sur l'organisation et la physiologie du poulpe, Bull. Acad. roy. de méd. de Belgique **46**:710, 1878.

11. Guillemet, R.: L'abaissement du taux du cuivre total du sang au cours de l'anémie expérimentale par saignées chez le chien, Compt. rend. Soc. de biol. **109**:221 (Jan.) 1932.

Copper markedly accelerates the spontaneous oxidation of iron in vitro. Quartaroli,[12] who made a thorough analysis of the relationship of copper to iron, observed this acceleration even in the presence of minute traces of copper. He was inclined to believe that the importance of iron in the organism as a respiratory ferment or inductor of oxidation in the tissues is chiefly dependent on its co-activation with copper. Furthermore, the oxidation of glutathione is accomplished by the action of copper as a catalyst, whereas iron and other metals fail in this capacity.[13] The importance of copper increases by virtue of this physiologic relationship to the inductors of oxidation and reduction processes in the body.

Hematopoiesis.—McHargue, Healy and Hill[14] drew attention to the importance of copper in the formation of hemoglobin and in the metabolism of animals having red blood cells. It was the intensive work, however, of Waddell, Steenbock, Elvehjem and Hart[15] which established copper as an essential factor in hematopoiesis. Their work has now been confirmed in many laboratories.

The mechanism by which copper catalyzes the formation of hemoglobin is not clear. Elvehjem's[16] experiments on yeast show that copper stimulates the formation of an iron complex, a-cytochrome. Since this pigment is related to the hemochromogens, which are derivatives of hemoglobin, the relationship of copper to the production of hemoglobin may depend in the animal organism on a similar activity of copper. Hill[17] has demonstrated that the administration of copper to animals results in a reduction in the amount of inorganic iron stored in the liver and in a corresponding increase in the organic form. The organic form of iron, he suggested, is the precursor of hemoglobin. Working on this suggestion, Cunningham[8] postulated a copper porphyrin which is converted into an iron porphyrin as the iron replaces the copper to form the hemoglobin molecule. Apparently copper is active in effecting the conversion of stored iron into the hemoglobinous

12. Quartaroli, A.: Il binomio ferro-rame in chimica e in biologia, Ann. di chim. applic. **22**:517, 1932.

13. Voegtlin, C.; Johnson, J. M., and Rosenthal, S. M.: Catalytic Action of Copper in Oxidation of Crystalline Glutathione, Pub. Health Rep. **46**:2234 (Sept. 18) 1931.

14. McHargue, J. S.; Healy, D. J., and Hill, E. S.: Relation of Copper to Hemoglobin Content of Rat Blood, J. Biol. Chem. **78**:637 (Aug.) 1928.

15. Waddell, J.; Steenbock, H.; Elvehjem, C. A., and Hart, E. B.: Iron in Nutrition: Further Proof that Anemia Produced on Diets of Whole Milk and Iron is Due to Deficiency in Copper, J. Biol. Chem. **83**:251 (July) 1929.

16. Elvehjem, C. A.: Rôle of Iron and Copper in Growth and Metabolism of Yeast, J. Biol. Chem. **90**:111 (April) 1931.

17. Hill, R.: Method for Estimation of Iron in Biological Material, Proc. Roy. Soc., London, s.B **107**:205 (Nov.) 1930.

form. In performing this function, copper tends to reduce the amount of iron stored in the reservoirs of the body. The work of Josephs [18] and of Elvehjem and Sherman [19] points to such a conclusion. On the other hand, this view was contested by Kletzein, Buchwald and Hudson,[20] who maintained that copper induces the retention of iron in the body. For several years Mallory [21] championed the latter contention in its application to the pathologic findings in hemochromatosis. These authors maintained that copper is the etiologic factor in this disease and, more specifically, that it is responsible for the deposits of hemosiderin granules containing iron in the body tissues. Reports from other laboratories are not in agreement with these findings.

It is widely accepted that copper in the presence of iron stimulates the regeneration of hemoglobin in animals made anemic by a milk diet. In addition, copper alone is also known to catalyze the formation of red cells.[22] Thus, animals receiving copper unsupplemented by iron show an increased erythrocyte level despite the low percentage of hemoglobin which persists. In the milk anemia, therefore, there is a specific deficiency of copper which must be corrected before the utilization of iron for the production of hemoglobin and before the formation of erythrocytes. It thus assumes a place in the list of deficiency anemias which occupy a prominent place in the recent literature. Already, attention is being focused on liver, iron, thyroxine, vitamin B_2, vitamin C and other substances the absence of any one of which results in a particular type of anemia. Clinicians have been reluctant, however, to accept copper as a specific therapeutic agent.

If anemia caused by a deficiency of copper exists, it seems logical to expect such a deficiency to be reflected in the blood stream by a diminished copper content. We determined the copper content of the blood of normal men and women and of patients with various pathologic conditions in an effort to study the problem more fully.

COPPER IN THE BLOOD

The distribution of copper among the various components of the blood has been studied by several investigators. Elvehjem, Steenbock

18. Josephs, W. H.: Studies on Iron Metabolism and Influence of Copper, J. Biol. Chem. **96**:599 (May) 1932.

19. Elvehjem, C. A., and Sherman, W. C.: Action of Copper in Iron Metabolism, J. Biol. Chem. **98**:309 (Oct.) 1932.

20. Kletzein, S. W.; Buchwald, K. W., and Hudson, L.: Mineral Metabolism —Copper and Iron, Proc. Soc. Exper. Biol. & Med. **30**:645 (Feb.) 1933.

21. Mallory, F. B.: Relation of Chronic Poisoning with Copper to Hemochromatosis, Am. J. Path. **1**:117 (Jan.) 1925.

22. Stein, H. B., and Lewis, E. C.: Stimulating Action of Copper on Erythropoiesis, J. Nutrition **6**:465 (Sept.) 1933.

and Hart,[23] Sarata [24] and Quartaroli [12] have found most of the copper of the blood to be present in the erythrocytes. In various other investigations in which a comparison of the copper content of the erythrocytes and that of the serum was made, the serum was found to possess the greater share of the total quantity present in the whole blood.[25] Guillemet [26] reported that the serum possesses almost the entire copper content of the blood. Our determinations of the copper content of the plasma and of the erythrocytes of dog blood reveal an equal distribution of the copper content of the whole blood between them. An illustration is given below:

	Copper, Mg.
10 cc. of whole blood	0.0091
Erythrocytes from 10 cc. of blood	0.0043
Plasma from 10 cc. of blood	0.0046
10 cc. of plasma	0.0099

Because of the differences reported in the copper content of the components of the blood, we feel justified in assuming that a reliable determination of the copper content of the blood can be made only on the whole blood.

Determination of Copper.—The modern trend in quantitative chemical examination of the blood is to employ a micromethod which is based on colorimetry. The colorimetric estimation of the copper content of the blood is made difficult by the presence of substances in the blood which interfere with the color produced by copper reagents. Iron, which is from three hundred to five hundred times more abundant than copper in the blood, is the chief offender. The use by other investigators of the blood serum instead of the whole blood has probably been an attempt to avoid the error introduced by the interfering iron.

Although many methods are available for the determination of copper in organic material, few are practicable for measuring accurately the minute quantities present in the blood. The ideal method should make possible the complete extraction of the copper, to which a sensitive reagent could then be applied to give quantitative results. However, the complete extraction of copper with avoidance of the interference of other blood elements is a difficult task. We spent much time and labor in the construction and use of a piece of apparatus, recently

23. Elvehjem, C. A.; Steenbock, H., and Hart, E. B.: Is Copper a Constituent of the Hemoglobin Molecule? J. Biol. Chem. **83**:21 (July) 1929.

24. Sarata, U.: Studies in the Biochemistry of Copper: II. The Copper Content of the Blood with a Method for Its Determination, Jap. J. M. Sc. Tr., II. Biochem. **2**:261 (Oct.) 1933.

25. Schindel, L.: Ueber den Kupfergehalt des Blutes, Klin. Wchnschr. **10**:743 (April 18) 1931.

26. Guillemet, R.: Sur le cuivre sanguin; sa répartition entre les différents constituants du sang normal, Compt. rend. Soc. de biol. **109**:652 (March) 1932.

described,[27] for the micro-electric separation of copper from the blood ash. In our hands the very small quantities of metal present in a convenient sample of blood could not be plated out successfully. Sarata [24] and Elvehjem and Lindow [28] have also discarded the electrolytic method because of its limited applicability.

The copper reagent which has gained the greatest popularity is sodium diethyl-di-thiocarbamate, described by Callan and Henderson.[29] A golden yellow color is produced, even with very minute quantities of copper. Warburg [30] originally suggested the use of pyrophosphate, which combines with iron to form an inactive compound that does not interefere with the determination of copper in the blood. In the method reported by McFarlane,[31] both the carbamate reagent and pyrophosphate are used. We followed the technic of McFarlane for the determinations of copper on the blood of the fifty normal men listed in table 1. However, we found that the iron is not completely bound by the pyrophosphate, even when large quantities of the reagent are added. As a result of the presence of unbound iron, the final color produced is often tinged brown instead of pure golden yellow. This interfering color renders difficult the comparison with the standard and is also apt to give higher results. In all other determinations reported in this paper we used the iron precipitation method described below.

METHODS

The determinations of iron and copper reported in this paper were made during the months from January to December 1933. The normal male subjects were freshman medical students, from 20 to 25 years of age, who had recently been examined and found in good health. The normal female subjects were nurses from 20 to 30 years of age and in good health.

Special precautions were taken to obtain pure reagents, free from copper and iron. Acids, alkalis and water were redistilled from glass and were tested at frequent intervals for contamination.

Blood counts were made with standardized pipets and counting chambers on blood drawn by cutaneous puncture of the lobe of the ear. In cases of severe anemia the count was checked on the venous blood.

Seven cubic centimeters of blood was drawn from the vein into a wide-mouthed tube containing 0.02 Gm. of sodium oxalate. The determinations on copper and iron were made shortly afterward.

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27. Clark, B. L., and Hermance, H. W.: Improved Apparatus for Micro-Electroanalysis, J. Am. Chem. Soc. **54**:877 (March) 1932.

28. Elvehjem, C. A., and Lindow, C. W.: Determination of Copper in Biochemical Materials, J. Biol. Chem. **81**:435 (Feb.) 1929.

29. Callan, T., and Henderson, J. A. R.: New Reagent for Colorimetric Determination of Minute Amounts of Copper, Analyst **54**:650 (Nov.) 1929.

30. Warburg, O.: Methode zur Bestimmung von Kupfer und Eisen und über den Kupfergehalt des Blutserums, Biochem. Ztschr. **187**:255, 1927.

31. McFarlane, W. D.: Application of the Sodium Diethyldithiocarbamate Reaction to the Micro-Colorimetric Determination of Copper in Organic Substances, Biochem. J. **26**:1022, 1932.

The determinations of iron were made on 0.5 cc. samples by a modified Wong method which we have already described.[32]

The determinations of copper were made as follows: Five cubic centimeters of blood was pipetted into an acid-washed copper-free vitreosil dish and dried on a hot plate with constant stirring. The dish was transferred to an electric muffle and for eight hours ashed at a low temperature. After cooling, the ash was moistened with 1 cc. of concentrated nitric acid and replaced on the hot plate to evaporate the excess acid. The ash was dissolved in 3 cc. of six times normal hydrochloric acid and was transferred quantitatively to a 15 cc. centrifuge tube. Two cubic centimeters of ammonia water containing 28 per cent of gaseous ammonia was pipetted into the tube, and the mixture was stirred until the gelatinous ferric hydroxide precipitate appeared throughout. The tube was then centrifugated at 1,500 revolutions per minute for twenty minutes.

The supernatant clear fluid was carefully poured off into a 25 cc. glass-stoppered cylinder, and the precipitate at the bottom of the centrifuge tube was redissolved by the addition of 0.8 cc. of six times normal hydrochloric acid. Five cubic centimeters of distilled water was used to wash down the sides of the tube in order to dilute the acid solution. The ferric hydroxide was reprecipitated by adding 0.5 cc. of ammonia water, and the tube was centrifugated for another twenty minutes. The clear supernatant fluid was combined with the first sample in the glass cylinder. Two cubic centimeters of a 0.5 per cent aqueous solution of the carbamate reagent was added, after which 4 cc. of amyl alcohol was accurately measured into each cylinder. The colored layer of alcohol was removed by means of a pipet and filtered into a microcup through an acid-washed 1 inch (2.5 cm.) filter paper. The filter paper removed the excess water.

A comparison was made with a standard solution containing 0.01 mg. of copper to which had been added the same quantities of each of the reagents as were added to the unknown sample. A blank was run with each series of determinations.

EXPERIMENTAL DATA ON IRON IN HUMAN BLOOD

Normal Iron Content.—The average iron content of the whole blood for the series of one hundred normal men listed in tables 1 and 2 was 50.25 mg. per hundred cubic centimeters of blood. The figure is in close agreement with the amount (50.01 mg.) which we reported for another series of one hundred normal men. The final average iron content based on determinations on blood from two hundred normal men was 50.13 ± 0.15 mg.[33] per hundred cubic centimeters.

The blood of fifty normal women, listed in table 3, averaged 44.11 mg. of iron per hundred cubic centimeters. This was slightly higher than the average figure (42.67 mg.) obtained in our previous series of fifty normal women. The final average iron content of the blood of one hundred normal women was 43.42 ± 0.19 mg. per hundred cubic centimeters.

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32. Sachs, A.; Levine, V. E., and Appelsis, A.: Iron in Human Blood, Arch. Int. Med. **52**:366 (Sept.) 1933.

33. This is the probable error of distribution. Thus, there is a fifty-fifty chance that the iron content of normal whole blood will fall somewhere within the range between average plus probable error and average minus probable error.

TABLE 1.—*Values for Copper and Iron in the Blood of Fifty Normal Men Aged 20 to 25* *

Name	Red Blood Cells	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Iron Index	Iron Color Index
1. Gre.	4,288,000	0.146	50.00	14.93	11.66	1.17
2. Del.	4,864,000	0.155	49.00	14.63	10.07	1.01
3. McG.	4,512,000	0.137	47.25	14.10	10.47	1.05
4. Lan.	4,832,000	0.128	48.55	14.49	10.05	1.00
5. Roc.	5,088,000	0.130	46.30	13.82	9.10	0.91
6. Bur.	4,960,000	0.153	46.55	13.90	9.39	0.94
7. Kab.	4,576,000	0.132	51.35	15.33	11.22	1.12
8. McL.	4,992,000	0.128	54.30	16.21	10.88	1.09
9. Mad.	4,736,000	0.127	49.35	14.73	10.42	1.04
10. Ran.	5,120,000	0.133	52.10	15.55	10.18	1.02
11. Whe.	5,184,000	0.135	55.85	16.67	10.77	1.08
12. Lov.	4,480,000	0.138	51.30	15.31	11.45	1.15
13. Jan.	4,704,000	0.163	45.45	13.57	9.66	0.97
14. Kan.	4,768,000	0.138	50.00	14.93	10.49	1.05
15. McC.	4,736,000	0.138	50.00	14.93	10.56	1.06
16. O'Fa.	4,480,000	0.133	47.85	14.28	10.68	1.07
17. O'Co.	4,256,000	0.135	50.85	15.18	11.95	1.20
18. Vit.	4,800,000	0.133	50.55	15.09	10.53	1.05
19. Pis.	4,544,000	0.138	48.35	14.43	10.64	1.06
20. Wat.	4,256,000	0.155	46.55	13.90	10.94	1.09
21. Fro.	4,512,000	0.146	52.10	15.55	11.55	1.16
22. Pav.	4,384,000	0.150	48.10	14.36	10.97	1.10
23. Dic.	4,704,000	0.135	50.50	15.08	10.74	1.07
24. Dol.	4,448,000	0.156	47.35	14.13	10.65	1.06
25. Cur.	4,160,000	0.149	49.20	14.69	11.83	1.18
26. Var.	4,896,000	0.156	53.20	15.88	10.87	1.09
27. Sil.	4,960,000	0.160	51.30	15.31	10.34	1.03
28. Sod.	4,576,000	0.135	54.65	16.31	11.94	1.19
29. Sem.	5,056,000	0.121	51.80	15.46	10.25	1.02
30. San.	4,672,000	0.149	53.20	15.88	11.39	1.14
31. Kar.	5,024,000	0.138	50.00	14.93	9.95	1.00
32. Fra.	4,928,000	0.150	54.45	16.25	11.05	1.10
33. Sul.	4,672,000	0.144	50.65	15.12	10.84	1.08
34. Tol.	4,832,000	0.154	50.45	15.06	10.44	1.04
35. Tuv.	5,280,000	0.142	48.30	14.42	9.15	0.92
36. Ell.	4,992,000	0.148	54.00	16.12	10.82	1.08
37. McF.	5,152,000	0.156	50.00	14.93	9.70	0.97
38. Ant.	4,998,000	0.137	50.20	14.99	10.04	1.00
39. Wei.	4,448,000	0.120	48.65	14.52	10.94	1.09
40. Mar.	4,448,000	0.140	46.50	13.88	10.45	1.05
41. Mar.	4,800,000	0.136	49.20	14.69	10.25	1.03
42. Man.	4,160,000	0.134	50.50	15.07	12.14	1.21
43. McC.	4,192,000	0.110	48.55	14.49	11.58	1.16
44. Bum.	4,832,000	0.146	50.00	14.93	10.35	1.04
45. Gra.	4,480,000	0.137	52.65	15.72	11.75	1.18
46. Num.	4,768,000	0.147	53.20	15.88	11.16	1.12
47. Bri.	4,448,000	0.160	50.20	14.99	11.29	1.13
48. Suz.	4,256,000	0.133	50.10	14.96	11.77	1.18
49. Thu.	4,224,000	0.121	51.30	15.31	12.14	1.21
50. Fle.	4,576,000	0.141	52.90	15.79	11.56	1.16
Average	4,681,000	0.141	50.29	15.01	10.78	1.08

* The values in the last three columns of this and the following tables (unless otherwise indicated) were determined by means of the following equations:

$$\text{Hemoglobin} = \frac{\text{milligrams of iron in 100 cc. of blood}}{3.35} = \text{grams of hemoglobin in 100 cc. of blood}$$

$$\text{Iron index} = \frac{\text{milligrams of iron in 100 cc. of blood}}{\text{first three figures of red blood cell count}}$$

$$\text{Iron color index} = \frac{\text{percentage of iron}}{\text{percentage of red blood cells}}, \text{ when } \begin{cases} 50 \text{ mg. of iron} = 100 \text{ per cent} \\ 5{,}000{,}000 \text{ red blood cells} = 100 \text{ per cent} \end{cases}$$

$$\text{therefore} = \frac{\text{milligrams of iron in 100 cc. of blood}}{\text{first two figures of red blood cell count}}$$

Helmer and Emerson,[34] using the same method, recently corroborated our results for the iron content of the whole blood of normal men. Their figure for the iron content of the whole blood of normal women, however, more nearly conforms with the average (44.11 mg.) of the

TABLE 2.—*Values for Copper and Iron in the Blood of Fifty Normal Men, Aged 20 to 25*

Name	Red Blood Cells	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Iron Index	Iron Color Index
1. And.	5,152,000	0.133	50.00	14.93	9.71	0.97
2. Bar.	4,928,000	0.134	50.00	14.93	10.15	1.01
3. Ben.	4,576,000	0.130	50.50	15.07	11.04	1.10
4. Bla.	4,640,000	0.125	51.00	15.22	10.99	1.10
5. Blo.	4,800,000	0.129	55.55	16.58	11.57	1.16
6. Bro.	4,704,000	0.124	49.00	14.63	10.42	1.04
7. Cam.	4,544,000	0.134	53.20	15.88	11.71	1.17
8. Can.	4,896,000	0.143	49.50	14.78	10.11	1.01
9. Chr.	4,860,000	0.132	47.35	14.13	9.74	0.97
10. Coy.	4,544,000	0.145	53.20	15.88	11.71	1.17
11. Col.	4,672,000	0.152	47.60	14.21	10.19	1.02
12. Die.	5,184,000	0.130	52.35	15.63	10.10	1.01
13. Cro.	4,896,000	0.140	49.00	14.63	10.01	1.00
14. Dav.	4,768,000	0.140	48.30	14.42	10.13	1.01
15. Dav.	4,832,000	0.136	51.00	15.22	10.55	1.06
16. Doo.	4,832,000	0.140	49.50	14.78	10.24	1.02
17. Dre.	4,512,000	0.141	47.85	14.28	10.61	1.06
18. Far.	4,512,000	0.133	46.10	13.76	10.22	1.02
19. Eck.	4,432,000	0.125	54.05	16.13	12.20	1.02
20. Fau.	5,120,000	0.131	50.00	14.93	9.77	0.98
21. Fis.	4,864,000	0.127	45.85	13.69	9.43	0.94
22. Fav.	4,480,000	0.126	46.10	13.76	10.29	1.03
23. Fra.	4,224,000	0.142	47.60	14.21	11.27	1.13
24. Fox.	4,416,000	0.132	51.30	15.31	11.62	1.16
25. Glo.	4,448,000	0.128	54.95	16.40	12.35	1.24
26. Gla.	4,480,000	0.130	50.50	15.07	11.27	1.13
27. Gla.	4,480,000	0.125	51.00	15.22	11.38	1.14
28. Gre.	4,736,000	0.132	48.90	14.60	10.32	1.03
29. Han.	4,800,000	0.132	49.25	14.70	10.26	1.03
30. Har.	4,768,000	0.135	51.00	15.22	10.70	1.07
31. Has.	4,736,000	0.140	51.00	15.22	10.77	1.08
32. Jac.	4,864,000	0.140	50.00	14.93	10.28	1.03
33. Irv.	5,024,000	0.139	51.30	15.31	10.21	1.02
34. Hal.	5,248,000	0.130	50.25	15.00	9.58	0.96
35. Het.	4,544,000	0.127	50.00	14.93	11.00	1.10
36. Pet.	4,318,000	0.133	50.00	14.93	11.58	1.16
37. Sma.	4,736,000	0.133	47.85	14.28	10.10	1.01
38. Pos.	4,608,000	0.126	51.00	15.22	11.07	1.11
39. Ric.	5,248,000	0.129	51.55	15.39	9.82	0.98
40. Saw.	4,736,000	0.141	47.60	14.21	10.05	1.01
41. Sac.	4,160,000	0.143	47.60	14.21	11.44	1.14
42. Tur.	5,120,000	0.139	52.65	15.72	10.03	1.00
43. Ste.	4,352,000	0.111	48.05	14.34	11.04	1.10
44. Swa.	4,544,000	0.120	51.55	15.39	11.34	1.13
45. McM.	4,800,000	0.120	50.05	14.94	10.43	1.04
46. Wic.	4,480,000	0.125	49.75	14.85	11.10	1.10
47. Mic.	4,896,000	0.110	52.90	15.79	10.80	1.08
48. O'Ne.	4,288,000	0.139	51.30	15.31	11.96	1.20
49. Pet.	4,704,000	0.121	52.35	15.63	11.13	1.11
50. O'Sh.	4,800,000	0.127	51.30	15.31	10.69	1.07
Average	4,706,000	0.132	50.19	14.98	10.69	1.07

present series (table 3) than with the 42.67 mg. which was the average for the earlier group of fifty women. Nevertheless, we do not believe that the higher results obtained in our last series of fifty women should replace those previously reported as being more nearly correct. In our large series of tests of the blood of normal women the range was wider

34. Helmer, O. M., and Emerson, C. P., Jr.: Iron Content of the Whole Blood of Normal Individuals, J. Biol. Chem. **104**:157 (Jan.) 1934.

TABLE 3.—*Values for Copper and Iron in the Blood of Fifty Normal Women, Aged 20 to 30*

Name	Red Blood Cells	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Iron Index	Iron Color Index*
1. Wur.	4,288,000	0.147	44.85	13.39	10.46	1.05
2. Cop.	4,672,000	0.137	44.20	13.19	9.46	0.95
3. Sue.	5,344,000	0.157	44.10	13.16	8.25	0.83
4. Mey.	5,142,000	0.113	45.60	13.61	8.87	0.89
5. Dul.	4,488,000	0.120	44.65	13.33	9.95	0.99
6. Dra.	4,896,000	0.134	42.00	12.54	8.58	0.86
7. Gla.	5,408,000	0.118	47.60	14.21	8.80	0.88
8. Bro.	4,124,000	0.141	38.90	11.61	9.43	0.94
9. Ful.	4,384,000	0.131	40.00	11.94	9.12	0.91
10. Dee.	5,056,000	0.160	43.10	12.87	8.52	0.85
11. Dah.	4,464,000	0.124	43.85	13.09	9.82	0.98
12. Fol.	4,768,000	0.136	45.05	13.45	9.45	0.95
13. Wil.	4,832,000	0.128	46.50	13.88	9.62	0.96
14. Jan.	4,960,000	0.142	41.30	12.33	8.33	0.83
15. Yos.	4,320,000	0.137	39.85	11.89	9.22	0.92
16. Det.	4,352,000	0.116	40.00	11.94	9.19	0.92
17. McK.	5,112,000	0.120	46.70	13.94	9.14	0.91
18. Tom.	4,960,000	0.140	46.30	13.82	9.34	0.93
19. Bux.	4,000,000	0.143	46.30	13.82	11.58	1.16
20. Woc.	4,204,000	0.129	44.85	13.39	10.67	1.07
21. Cla.	4,544,000	0.124	46.70	13.94	10.28	1.03
22. Lis.	4,420,000	0.120	45.45	13.57	10.28	1.03
23. And.	4,512,000	0.128	43.30	12.93	9.59	0.96
24. Bye.	4,288,000	0.128	41.85	12.49	9.76	0.98
25. Her.	4,160,000	0.130	45.65	13.63	10.97	1.10
26. Ste.	4,224,000	0.137	46.45	13.87	11.00	1.10
27. Lyo.	4,416,000	0.133	45.45	13.57	10.29	1.03
28. Hug.	4,160,000	0.133	39.85	11.90	9.58	0.96
29. Mil.	4,224,000	0.137	46.10	13.76	10.91	1.09
30. All.	4,320,000	0.121	43.10	12.87	9.98	1.00
31. Sta.	4,288,000	0.118	41.15	12.28	9.60	0.96
32. Gle.	4,544,000	0.122	45.05	13.45	9.91	0.99
33. Poh.	4,352,000	0.145	46.00	13.73	10.57	1.06
34. Ken.	4,950,000	0.126	45.05	13.45	9.10	0.91
35. Mey.	4,460,000	0.130	45.45	13.57	10.19	1.02
36. Voi.	4,410,000	0.144	42.75	12.76	9.69	0.97
37. Kel.	5,000,000	0.127	46.10	13.76	9.22	0.92
38. Mel.	3,875,000	0.137	40.65	12.13	10.49	1.05
39. Tho.	4,620,000	0.128	46.50	13.88	10.07	1.01
40. McC.	4,160,000	0.127	44.45	13.27	10.69	1.07
41. Lan.	4,850,000	0.130	44.05	13.15	9.08	0.91
42. Bur.	4,265,000	0.135	41.85	12.49	9.81	0.98
43. Hil.	4,770,000	0.132	44.50	13.28	9.33	0.93
44. Bob.	5,000,000	0.121	45.30	13.52	9.06	0.91
45. Bul.	4,850,000	0.120	46.50	13.88	9.59	0.96
46. Kel.	4,228,000	0.127	44.65	13.33	10.56	1.06
47. Jor.	3,776,000	0.160	46.50	13.88	12.31	1.23
48. All.	4,450,000	0.146	45.45	13.57	10.21	1.02
49. McC.	4,950,000	0.121	46.95	14.01	9.49	0.95
50. Jos.	4,000,000	0.112	39.50	11.79	9.88	0.99
Average	4,560,000	0.131	44.11	13.18	9.79	0.98

* Iron color index $= \dfrac{\text{percentage of iron}}{\text{percentage of red blood cells}}$ when $\begin{cases} \text{45 mg. of iron} = \text{100 per cent} \\ \text{4,500,000 red blood cells} = \text{100 per cent} \end{cases}$

therefore $= \dfrac{\text{milligrams of iron in 100 cc. of blood}}{\text{first two figures of red blood cell count}}$

TABLE 4.—*Values for Iron and Copper in the Blood of Normal Men and Women*

Group	Red Blood Cell Count	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Iron Index	Iron Color Index
A. 50 men	4,681,000	0.141*	50.29	15.01	10.78	1.08
B. 50 men	4,706,000	0.132*	50.19	14.98	10.69	1.07
C. 50 men	4,963,520	.....	51.05	15.25	10.32	1.03
D. 50 men	5,045,280	.....	48.97	14.62	9.71	0.97
Average	4,879,160	.....	50.13	14.96	10.37	1.04
E. 50 women	4,560,000	0.131	44.16	13.18	9.79	0.98
F. 50 women	4,457,000	.....	42.67	12.74	9.59	1.01
Average	4,508,500	.....	43.42	12.96	9.69	0.99

* Different methods were used in estimating the copper content of groups A and B.

and the variability was greater than that for normal men. We feel that this fluctuation in the iron content is the result of the instability of the female hematopoietic system. Such a view is in harmony with the findings of Bloomfield and Pollard.[35] In a comparison of the blood values of normal men and women, the latter showed a greater incidence of achlorhydria, which may account for the greater tendency toward the anemic state in women.

For clinical purposes, the mathematical index, the mode, which represents the figure that appears most frequently in a series and around which the majority of the figures are grouped, is a better guide than the average. The mode for the one hundred normal women was 45 mg. of iron, while the mode for the two hundred normal men remained the same as the average, 50 mg.

Hemoglobin.—Since the publication of our report on the iron content of human blood, several papers have appeared on the same subject.[36] These investigations confirm our conclusions that hemoglobinometers may be standardized by the use of the figures for the iron content of the blood. Using the factor [37] $\text{hemoglobin} = \frac{\text{milligrams of iron in 100 cc. of blood}}{3.35}$ the amount of hemoglobin in grams per hundred cubic centimeters of blood may be estimated from the iron content of the whole blood. Clinical hemoglobinometers have as their standard for 100 per cent figures which range from 13 to 17 Gm. of hemoglobin per hundred cubic centimeters of blood. Our large series of figures for the blood iron of normal men and women is also of value in establishing normal standards for the hemoglobin content.

The average hemoglobin content for two hundred normal men was 14.96 ± 0.045 Gm. per hundred cubic centimeters of blood. The average hemoglobin for one hundred normal women was 12.96 ± 0.06 Gm.

In the determination of the percentage of hemoglobin by most clinical methods one standard is employed for both men and women. It is obvious from the marked difference between the iron content of the blood of normal men and that of normal women that the percentage of hemoglobin for the two sexes is also widely separated. The corrected averages, the modes, which were 50 mg. of iron per hundred cubic centimeters of blood for normal men and 45 mg. for normal women, emphasize this difference.

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35. Bloomfield, A. L., and Pollard, W. S.: Gastric Anacidity: Its Relation to Disease, New York, The Macmillan Company, 1933.

36. Dowden, C. W., and McNeill, C.: Clinical Study of Blood Iron and Hemoglobin, J. Lab. & Clin. Med. **19**:362 (Jan.) 1934. Haden, R. L.: Determination of Hemoglobin by the Iron Content Method, ibid. **19**:406 (Jan.) 1934.

37. Butterfield, E.: Ueber die Lichtextinktion, das Gasbindungsvermögen und den Eisengehalt des menschlichen Blutfarbstoffs in normalen und krankhaften Zuständen, Ztschr. f. physiol. Chem. **62**:173, 1909

The figure 50 mg. for normal men lends itself admirably for clinical use. This represents 100 per cent of iron. Since the hemoglobin is a multiple of iron, one may state that 50 mg. of iron corresponds to 100 per cent of hemoglobin. In general, then, the number of milligrams of iron per hundred cubic centimeters of blood of a man may be conveniently converted into the percentage of hemoglobin by multiplying by 2. If this formula is applied to the mode for women (45 mg. of iron) the hemoglobin content of the average woman is only 90 per cent. Herein lies the disadvantage of the use of a single standard for the estimation of the hemoglobin content for both sexes. By its use the figure 80 per cent of hemoglobin would represent a similar level for both sexes, whereas it is obvious from our figures that such a concentration of hemoglobin would actually represent a more anemic level in a man than in a woman. If the scale of 100 per cent of hemoglobin is to be retained for both sexes the number of milligrams of iron per hundred cubic centimeters of blood for women must be multiplied by 2.22 to correspond with the number of milligrams of iron per hundred cubic centimeters of blood multiplied by 2 for men.

Iron Color Index.—The iron index of Murphy, Lynch and Howard [38] is obtained as follows:

$$\frac{\text{milligrams of iron in 100 cc. of blood}}{\text{red blood cells in millions}} = \text{iron index}$$

We suggested [32] the iron color index, $\frac{\text{percentage of iron}}{\text{percentage of red blood cells}}$, for use "in order to retain the convenient $+1$ and -1 of the older color index and yet take advantage of the greater accuracy of the iron index." If one makes use of the modes, the iron color index becomes further simplified. Thus, 50 mg. of iron and 5,000,000 red blood cells become the standards or 100 per cent levels for men, while 45 mg. of iron and 4,500,000 red blood cells represent 100 per cent levels for women. To illustrate: The iron color index of a man with an iron content of the blood of 40 mg. per hundred cubic centimeters and an erythrocyte count of 4,800,000 would be $\frac{\text{percentage of iron}}{\text{percentage of red blood cells}} = \frac{80}{96} = -1$. Since in this equation both the iron content and the first two figures of the red blood cell count must be divided by 50 to determine the percentage of the normal of each, then

$$\frac{\text{percentage of iron}}{\text{percentage of red blood cells}} = \frac{\text{milligrams of iron in 100 cc. of blood}}{\text{first two figures of red blood cell count}} = \frac{40}{48} = -1.$$

For women both figures are divided by 45, and therefore the same formula obtains. Consequently, the iron color index based on our figures for the iron content of the blood of both sexes may be calculated simply by dividing the number of milligrams of iron per hundred cubic centimeters of blood by the first two figures of the erythrocyte count.

38. Murphy, W. P.; Lynch, R., and Howard, I. M.: Value of Determinations of Iron Content of Whole Blood, Arch. Int. Med. **47**:883 (June) 1931.

Total Amount of Iron in the Blood Stream.—The figure 3 Gm. of iron is often quoted as representing the total amount of iron present in the body. On the basis of 50 mg. of iron per hundred cubic centimeters of blood and 85 cc. of blood per kilogram of body weight, a man weighing 70 Kg., possessing approximately 6 liters of blood, has in the blood stream alone 3 Gm. of iron. The total amount of iron in the body, if one includes the iron stored in the reservoirs, the liver and the spleen as well as the iron present in the nucleus of every cell in the body, is therefore more than this figure. A woman weighing 55 Kg., possessing 4.7 liters of blood, would have approximately 2 Gm. of iron in the blood stream, taking 45 mg. of iron per hundred cubic centimeters of blood as the standard.

EXPERIMENTAL DATA ON COPPER IN HUMAN BLOOD

Normal Copper Content.—The series of one hundred and fifty determinations used to establish the average copper content of whole blood represents, so far as we know, the most substantial number reported in the literature.

The average copper content of the blood of the fifty normal men listed in table 1 was 0.141 mg. or 141 micrograms per hundred cubic centimeters. The McFarlane [31] technic was employed in making this group of determinations. We have explained the difficulties encountered in the use of this method as well as our reasons for believing the results obtained to be somewhat high. We therefore employed the iron precipitation method for all the other determinations of copper reported.

The copper content of the blood of the fifty normal men listed in table 2 averaged 0.132 ± 0.0008 mg. per hundred cubic centimeters of blood. We have adopted this figure as the standard for normal men.

The figures for the blood copper of the fifty normal women listed in table 3 averaged 0.131 ± 0.0012 mg. per hundred cubic centimeters. Unlike the variations in the blood iron, the figures for the blood copper of the two sexes approximated each other. With regard to normal women we have already referred to the tendency toward the anemic state, a fact which explains the fluctuation in the iron content of their blood. Our studies on anemia, which we report later, lead us to think that there exists a reciprocal relationship between the iron and the copper content of the blood. As a rule, when we found a low iron content we found a high copper content. We are therefore inclined to the belief that the greater potentiality of anemia to develop in women probably calls out of reserve a greater quantity of hematopoietic stimulant in the form of copper. This mechanism may account for the presence in the blood of women of a larger quantity of copper in proportion to iron than is found in the blood of men. This also aids in interpreting the frequent finding of a high copper level coupled with a normal iron level in routine determinations on female patients.

Total Copper in the Blood Stream.—The average man weighing 70 Kg. has approximately 7.8 mg. of copper in the blood stream. The figure for a woman weighing 55 Kg. is approximately 6 mg. of copper. The ratio of the total iron to the total copper of the blood is $\frac{3,000}{7.8}$, or 385 : 1, for the man and $\frac{2,000}{6}$, or 333 : 1, for the woman. These figures demonstrate that the blood copper of the average woman is greater in proportion to the blood iron than is the blood copper of the average man.

SUMMARY

Copper.—The copper content of the whole blood of normal men has been determined by two methods. By one method we obtained an average for fifty normal men of 0.141 mg., or 141 micrograms, of copper per hundred cubic centimeters of blood. By a second method we obtained an average for another series of fifty normal men of 0.132 ± 0.0008 mg.

We have adopted the latter figure as the normal because we have reason to believe that the method employed in the second series of determinations can be better controlled. The figures reported for the blood copper of normal women are also based on the latter method.

The average copper content of the whole blood of fifty normal women was 0.131 ± 0.0012 mg. per hundred cubic centimeters.

Although there is a marked difference between the iron content of the whole blood of normal men and that of normal women, no such difference existed for the blood copper. The blood copper is greater in proportion to the blood iron in women than in men. This is in harmony with the observation that women are more susceptible to anemia than are men. This greater susceptibility calls forth a relatively greater amount of copper to stimulate hematopoiesis.

Iron.—The average iron content of the whole blood for two hundred normal men was 50.13 ± 0.15 mg. per hundred cubic centimeters, and for one hundred normal women, 43.42 ± 0.19 mg.

The mathematical index, the mode, the figure which appears most frequently in the series of determinations and around which the majority of the figures group themselves, was 50 mg. of iron per hundred cubic centimeters for the two hundred normal men and 45 mg. for the one hundred normal women.

The fact that in women the average fell below the mode illustrates the tendency toward the anemic state in normal women.

We wish to emphasize further the accuracy with which the hemoglobin content may be estimated from the figures for the iron content and the facility with which hemoglobinometers may be standardized by the use of the method of determining the iron content.

On the basis of the fact that hemoglobin contains 0.335 per cent of iron, the average whole blood of normal men contains 14.96 ± 0.045 Gm. of hemoglobin per hundred cubic centimeters, while the average whole blood of normal women contains 12.96 ± 0.06 Gm.

Instead of the single standard for hemoglobin now employed clinically for both men and women, it would be more accurate to use one standard for men and another for women.

Since the normal iron content for men is 50 mg. per hundred cubic centimeters, one may state that this figure represents 100 per cent of hemoglobin. One can therefore convert with ease the iron content of the blood into the percentage of hemoglobin by multiplying the figure for the iron content per hundred cubic centimeters by 2. In the case of women, however, this conversion entails the multiplication of the figure for iron by 2.22, since the normal iron content of the blood of the average woman is 45 mg. per hundred cubic centimeters.

The iron color index, which may be substituted with greater accuracy for the old color index, may be obtained by dividing the number of milligrams of iron per hundred cubic centimeters of blood by the first two figures of the red blood cell count. This derivation of the index is based on our figures for the normal iron content of the whole blood of both sexes.

II. BLOOD COPPER AND IRON IN MEN AND WOMEN WITH VARIOUS PATHOLOGIC CONDITIONS

Having determined the copper and the iron content of the whole blood of adult normal men and women, and using these figures as standards for comparison, we examined the blood of patients suffering from various diseases.

The copper and the iron content of the whole blood, the red cell count, the percentage of hemoglobin, the iron index and the iron color index of thirty-two patients suffering from various diseases which tend to produce abnormal blood pictures are listed in table 5. Among the group were patients with: pernicious anemia (treated and untreated), Banti's disease, acute myelogenous leukemia, chronic lymphatic leukemia, malaria, gastric hemorrhage, arsenic poisoning, nephritis and carcinoma.

This study was undertaken to ascertain whether anemia due to a deficiency of copper occurs in man. The figures in table 5 show definitely that pathologic conditions associated with anemia are characterized by a high copper content of the blood. We have adopted the term "hypercupremia," to indicate such an increased copper level. In all our determinations thus far, we have not encountered hypocupremia in any pathologic condition.

Generally speaking, we have observed an inverse relationship between the blood copper and the blood iron with a possible exception in nephritis. When the iron content was low, the copper con-

tent was high. The lower the figure we obtained for the blood iron, the higher the figure we could expect for the blood copper. Such a relationship is illustrated by the following findings: in patient 16 (with sickle cell anemia), blood iron, 24.51 mg., blood copper, 0.235 mg.; in patient 17 (with Banti's disease), blood iron, 27.25 mg., blood copper, 0.187 mg.; in patient 19 (with acute myelogenous leukemia), blood iron, 32.90 mg., blood copper, 0.24 mg.; in patient 12 (with secondary anemia), blood iron, 39.05 mg., blood copper, 0.172 mg., and

TABLE 5.—*Values for Copper and Iron in the Blood of Patients with Various Pathologic Conditions*

Name	Sex	Diagnosis	Red Blood Cells	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Iron Index	Iron Color Index
1. Bow.	F	Pernicious anemia (treated).....	4,200,000	0.170	41.30	12.33	9.83	0.98
2. Foy.	M	Pernicious anemia (treated).....	4,015,000	0.139	42.65	12.73	10.62	1.06
3. Sis.	F	Pernicious anemia (treated).....	2,490,000	0.136	41.30	12.33	16.59	1.66
4. Sla.	M	Pernicious anemia (treated).....	1,990,000	0.180	35.45	10.58	17.81	1.78
5. Hei.	M	Pernicious anemia (untreated)..	1,810,000	0.164	20.00	5.97	11.05	1.11
6. Boc.	F	Pernicious anemia (untreated)..	1,350,000	0.201	16.40	4.90	12.15	1.21
7. Pot.	F	Pernicious anemia (untreated)..	2,850,000	0.198	38.15	11.39	13.39	1.34
8. Gar.	M	Secondary anemia.....	3,300,000	0.173	29.65	8.85	8.98	0.90
9. Cal.	M	Secondary anemia.....	3,968,000	0.222	42.00	12.54	10.59	1.06
10. Wes.	F	Secondary anemia.....	3,968,000	0.180	31.65	9.45	7.98	0.80
11. Gow.	F	Secondary anemia.....	3,200,000	0.198	28.56	8.52	8.91	0.89
12. All.	M	Secondary anemia.....	3,750,000	0.172	39.05	11.66	10.41	1.04
13. Cre.*	M	Secondary anemia.....	4,224,000	0.167	35.45	10.58	8.39	0.84
14. Cre.*	M	Secondary anemia.....	4,416,000	0.155	41.15	12.28	9.32	0.93
15. Wic.	F	Secondary anemia.....	3,904,000	0.174	31.55	9.42	8.08	0.81
16. Bas.	M	Sickle cell anemia.....	2,520,000	0.235	24.51	7.32	9.74	0.97
17. Cam.	F	Banti's anemia.....	3,850,000	0.187	27.25	8.13	7.08	0.71
18. Mic.	F	von Jaksch's anemia.....	3,230,000	0.211	35.20	10.51	10.90	1.09
19. Mik.	M	Acute myelogenous leukemia....	3,250,000	0.240	32.90	9.82	10.12	1.01
20. Mah.	M	Chronic lymphatic leukemia.....	4,672,000	0.160	52.65	15.72	11.27	1.13
21. Lis.	F	Chronic lymphatic leukemia.....	3,770,000	0.187	40.30	12.03	10.69	1.07
22. Mal.	M	Malaria.....	3,475,000	0.158	39.05	11.66	11.24	1.12
23. Kul.	M	Purpura.....	3,230,000	0.195	36.35	10.85	11.25	1.13
24. Joh.	M	Arsenic poisoning.....	1,715,000	0.254	21.20	6.33	12.36	1.24
25. McG.*	M	Nephritis.....	2,665,000	0.180	30.95	9.24	11.61	1.16
			1,880,000	0.145	22.05	6.58	11.73	1.17
26. And.	M	Gastric hemorrhage.....	4,162,000	0.162	42.35	12.64	10.18	1.02
27. Die.	F	Neurasthenia.....	4,288,000	0.162	39.85	11.90	9.29	0.93
28. Mor.	F	Carcinoma of the ovary.....	3,968,000	0.150	44.45	13.27	11.20	1.12
29. Fri.	F	Carcinoma of the ovary.....	4,252,000	0.176	38.45	11.48	9.04	0.90
30. St. J.	M	Carcinoma of the rectum.....	2,945,000	0.200	20.20	6.03	6.86	0.69
31. Law.	M	Carcinoma of the rectum.....	4,544,000	0.172	38.75	11.57	8.53	0.85
32. Joy.	F	Carcinoma of the breast.....	3,968,000	0.274	32.80	9.79	8.27	0.83
33. Wea.	F	Carcinoma of the uterus.....	3,710,000	0.168	31.95	9.54	8.61	0.86

* Two determinations were made on this patient.

in patient 21 (with chronic lymphatic leukemia), blood iron, 40.3 mg., blood copper, 0.187 mg. Patient 20, with chronic lymphatic leukemia, showed hypercupremia despite a normal value of blood iron.

Patient 25, with chronic nephritis, showed the typical relationship of iron to copper which characterizes the anemic state with an iron content of 30.95 mg. and a copper content of 0.18 mg. At a later date, despite the development of more severe anemia, represented by a blood iron content of 22.05 mg., the blood copper did not show the anticipated increase, but actually fell to 0.145 mg. In another patient with chronic nephritis (Miss S, for whom figures are not included in table 5), an iron content of 33.9 mg. was accompanied by a copper content of 0.123 mg.

We are continuing the studies on the copper metabolism in chronic nephritis in an attempt to find an explanation for the discrepancies in the values for persons with this condition.

With reference to our findings, we note that Warburg and Krebs [39] mentioned an increase in the copper content of the serum of pigeons that were bled. Sheldon and Ramage,[40] examining twenty-eight specimens of human blood spectroscopically, observed the strongest copper lines in the blood of a patient with anemia following hemorrhage and in that of a patient with carcinoma. In seven cases of anemia in children, Gorter, Grendel and Weyers [41] found an elevated copper level in the whole blood. The serum copper level was also high in several cases of anemia reported by Locke, Main and Robash.[42] None of these investigators, however, determined the copper content of the whole blood with relation to the iron content of the whole blood.

The work of Gorter, Grendel and Weyers deserves special comment, for they are the only investigators who reported copper determinations on the whole blood in anemia. Their determinations were made by the use of the electrolytic method for the separation of copper. Sarata [24] and Elvehjem and Lindow [28] discarded this method because of the failure to obtain accurate results when small samples of blood were used. Flinn and Inouye [7] electrolyzed the material for twenty-four hours in order to plate out all of the copper from blood ash. Using a micro-electrolytic apparatus, we were unable to plate out more than 70 per cent of the copper in twelve hours. Gorter and his associates, however, claimed 100 per cent accuracy with the electrolytic method run for twenty minutes.

COPPER AND IRON IN THE BLOOD OF A PATIENT WITH POLYCYTHAEMIA VERA

Our blood findings for a patient with polycythaemia vera serve to verify the inverse relationship between copper and iron. Before treatment with phenylhydrazine was instituted, this patient, a woman, 60 years of age, had a normal value for copper in the blood despite an abnormally elevated erythrocyte count and a high value for iron. After a few weeks of treatment with phenylhydrazine, marked changes in the

39. Warburg, O., and Krebs, H. A.: Ueber locker gebundenes Kupfer und Eisen im Blutserum, Biochem. Ztschr. **190**:143, 1927.

40. Sheldon, S. H., and Ramage, H.: Spectrographic Analysis of Human Tissues, Biochem. J. **25**:1608, 1931.

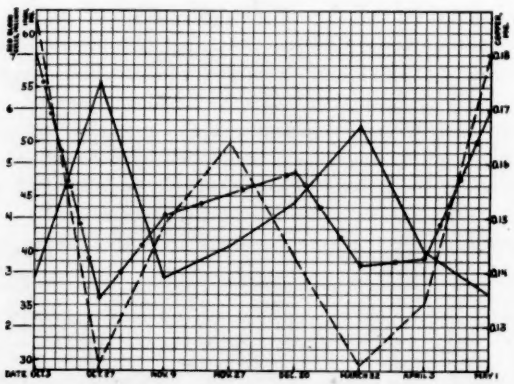
41. Gorter, E.; Grendel, F., and Weyers, W. A. M.: Le rôle du cuivre dans l'anémie infantile, Rev. franç. de pédiat. **7**:747, 1931.

42. Locke, A.; Main, E. R., and Robash, D. O.: Copper and Non-Hemoglobinous Iron Contents of Blood Serum in Disease, J. Clin. Investigation **11**:527 (May) 1932.

blood picture were observed. While the erythrocyte count and iron content fell sharply, the copper content of the blood rose. The drug was then omitted, and liver and iron were administered. As a result, the red blood cell count and the iron content of the blood rose, while the copper content fell.

TABLE 6.—*Red Blood Cell Count and Copper and Iron Content of the Whole Blood in a Patient with Polycythaemia Vera*

Date	Red Blood Cells	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc.	Comment
10/ 3/33	7,040,000	0.139	60.95	Treatment with phenylhydrazine begun
10/27/33	2,592,000	0.175	29.40	Treatment stopped
11/ 9/33	4,063,000	0.139	42.50	
11/29/33	4,416,000	0.145	50.00	Treatment resumed
12/20/33	4,896,000	0.153	39.37	
3/28/34	3,072,000	0.167	29.55	Treatment stopped
4/ 3/34	3,296,000	0.144	35.20	
5/ 1/34	5,952,000	0.136	37.80	



A graph showing the fluctuation in values for iron and copper in the blood of a patient with polycythaemia vera. The broken line with the open circles represents the red blood cell count in millions per cubic millimeter of blood; the solid line represents the values for copper in milligrams per hundred cubic centimeters of blood, and the broken line represents the values for iron in milligrams per hundred cubic centimeters of blood.

The fluctuations in the red cell count and in the iron and the copper content of the blood in periods of treatment with phenylhydrazine and in periods in which treatment was not given are illustrated in the chart.

COPPER AND IRON IN THE BLOOD OF PATIENTS WITH TUBERCULOSIS

We have determined the copper and the iron content of the blood of ten men and ten women suffering from tuberculosis. The findings are listed in tables 7 and 8.

The tuberculous patients were in a sanatorium and had been under treatment for some time when samples of blood were drawn for analysis. Patient 1 in the series of men had a normal iron and copper content of the blood. His was classed as an arrested case, and he was about to be discharged. Patients 5 and 9 in the group of women and patients 2, 4, 5 and 6 in the group of men had a normal iron content, but the copper content was high. All the other patients showed a low

TABLE 7.—*Values for Copper and Iron in the Blood of Ten Men with Tuberculosis*

Name	Red Blood Cells	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Iron Index	Iron Color Index
1. Now.	4,550,000	0.129	52.15	15.57	11.46	1.15
2. Fra.	5,000,000	0.154	51.30	15.31	10.26	1.03
3. Jen.	4,700,000	0.163	47.35	14.13	10.07	1.01
4. Wel.	4,510,000	0.179	51.10	15.25	11.33	1.10
5. Swa.	5,000,000	0.169	49.50	14.78	9.90	0.99
6. O'Sh.	4,530,000	0.171	49.00	14.63	10.82	1.08
7. Wad.	4,280,000	0.207	43.45	12.97	10.15	1.02
8. Kom.	4,680,000	0.208	44.25	13.21	9.46	0.90
9. Ang.	3,950,000	0.207	42.00	12.54	10.63	1.06
10. Cla.	4,200,000	0.234	38.30	11.43	9.12	0.91
Average	4,540,000	0.182	46.84	13.98	10.32	1.03

TABLE 8.—*Values for Copper and Iron Determined on the Blood of Ten Women with Tuberculosis*

Name	Red Blood Cells	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Iron Index	Iron Color Index
1. Wig.	4,030,000	0.225	38.15	11.39	9.46	0.95
2. Min.	3,700,000	0.222	38.75	11.57	10.47	1.05
3. Hic.	4,420,000	0.247	40.65	12.13	9.20	0.92
4. For.	4,210,000	0.186	41.30	12.33	9.81	0.98
5. Mic.	4,480,000	0.163	46.10	13.76	10.29	1.03
6. Con.	4,250,000	0.216	40.45	12.08	9.52	0.95
7. Wil.	4,025,000	0.183	38.48	11.49	9.56	0.96
8. Swa.	4,050,000	0.174	42.35	12.64	10.46	1.05
9. Hun.	4,200,000	0.154	48.55	14.49	11.56	1.16
10. McC.	3,700,000	0.183	39.20	11.70	10.59	1.06
Average	4,107,000	0.195	41.40	12.36	10.09	1.01

iron level and a high copper level. The hypercupremia in the series of tuberculous patients was characteristic of disease syndromes in which chronic sepsis and fever are present. It may have been the result of the failure on the part of the liver or bone marrow to store or utilize the metal. The anemia of tuberculosis may be the result of hemorrhage, but it is usually myelophthisic; that is, it arises from a depression of the bone marrow. If the bone marrow is depressed, the utilization of copper may also be inhibited, thus accounting for the increased amounts remaining in the circulation.

The hypercupremia in tuberculous patients may, on the other hand, be a mobilization of copper for purposes of catalysis. What associations the increased copper level has with respiration and with

various processes of oxidation and reduction is problematic. The relationship to hematopoiesis is more apparent. From an examination of the figures, especially those for the male patients, the copper level seems to be definitely linked with the severity of the anemia or with the iron level. The hypercupremia of tuberculosis may therefore coincide with the inverse relationship of copper to iron, which is characteristic of anemia.

COMMENT

In milk anemia of rats, copper in the presence of iron is effective, when used in small doses, in increasing the hemoglobin concentration and the red blood cell count. Since copper is not part of the hemoglobin molecule, Elvehjem, Steenbock and Hart [23] maintained that this metal functions as a catalyst. Its presence makes possible the utilization of the building stones, iron and protein, necessary for the manufacture of hemoglobin and erythrocytes. Since all the other factors necessary for hematopoiesis are present, the result is especially dramatic when the deficiency is corrected by the addition of copper. Equally striking is the reaction in the anemia of pellagra, which is amenable only to treatment with vitamin B_2, of scurvy, which responds only to the administration of vitamin C, and of hypothyroidism, which is corrected only by the administration of thyroid. If, on the other hand, a building stone is missing, as in the deficiency of protein in famine anemia and in the deficiency of iron in primary hypochromic anemia, the response is slower and is dependent on the quantity and frequency of intake of the missing factor.

Is copper a specific requirement for man? One cannot always apply the results of experimentation on animals to man. Even the work of Whipple and Robscheit-Robbins [43] on the hemorrhagic anemia of dogs, which anticipated the discovery of the specificity of liver for pernicious anemia, is as yet not directly applicable to man. Pernicious anemia is not a disease of dogs. The stomach and liver of the dog contain very little of the substances effective in the treatment of pernicious anemia in man.[44]

Copper falls into the category of hematopoietic catalysts, which includes thyroxine, vitamins B_2 and C and sunshine and possibly other factors which have not been discovered. Beard, Johnson and Andes [45]

43. Whipple, G. H., and Robscheit-Robbins, F. S.: Simple Experimental Anemia and Liver Extracts, Proc. Soc. Exper. Biol. & Med. **24**:860 (June) 1927.

44. Richter, O.; Ivy, A. C., and Meyer, A. F.: A Study of the Dog's Stomach and Liver for Substances Effective in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **31**:550 (Feb.) 1934.

45. Beard, H. H.; Johnson, A. G., and Andes, E. J.: Effect of Radiant Energy With and Without Iron upon Nutritional Anemia in the Rat, Proc. Soc. Exper. Biol. & Med. **31**:23 (Oct.) 1933.

corrected the anemia of rats on copper-free milk diets by the use of sunshine and iron. This opens a new avenue of thought with respect to these catalysts. It may be possible that the effect produced by any one may be replaced by another.

The habitat of the rat family is essentially devoid of sunlight. The importance of copper in the rat's hematopoietic system may be an adaptation, just as the ability of this animal to manufacture vitamin C is a characteristic born of necessity. Early experimentation immediately stamped the rat unfit for studies on vitamin C. In this animal, belonging to a scavenger family which infrequently feeds on fresh foods, there has developed this faculty of intrinsic preparation of this essential with which other animals and man must be supplied ready for use in the form of antiscorbutic foods. An analogous situation may exist with regard to the importance of copper in the rat as compared with the need for it in man. The figures of Warburg and Krebs [89] on the copper content of the serum of various animals show that the rat possesses the highest copper level. This further emphasizes the possible need in the case of the rat for a high copper content of the blood to substitute for other hematopoietic catalysts.

The conditions of the experiments on animals in which copper was shown to be a requirement are also highly artificial and give promise of little practical application to studies on human beings. Even the iron salts in the diet were specially purified to avoid contamination by copper. Parsons [46] stated that clinically when iron fails to correct anemia the addition of copper is of no avail because of the usual presence of recognizable quantities of copper in iron salts. We know from our experience with reagents and even with distilled water that traces of copper are always present. We have found copper in ordinary drinking water. A diet which includes vegetables, fruits, liver and other internal organs, sea foods and pasteurized milk is comparatively rich in copper. Although this fact does not rule out any important rôle that copper may play when it is ingested, it at least indicates that a copper-free or even a copper-poor diet is possible only in a person on a very restricted intake.

Even though the copper intake is low, a sufficient supply is maintained through the quantities of the metal stored in the liver and in other organs. This is true for a human being more than for a rat in the experimental cage. Recognizing this fact, Schultze and Elvehjem [47] recently accounted for the failure of copper to assume greater importance in the clinical treatment of anemia by citing the large quantities

46. Parsons, L. G.: Anemias of Infancy and Early Childhood; Some Observations, J. A. M. A. **97**:973 (Oct. 3) 1931.

47. Schultze, M. O., and Elvehjem, C. A.: The Relation of Iron and Copper to the Reticulocyte Response in Anemic Rats, J. Biol. Chem. **102**:357 (Oct.) 1933.

stored by man. This was evident in our studies of the blood copper in cases of blood dyscrasia in which, despite the existence of long-standing anemia, hypercupremia was maintained.

The most likely conclusion to be drawn from the finding of a high copper content in almost all cases of anemia is that the copper is brought into use from the body reservoirs to stimulate hematopoiesis. Other possibilities suggest themselves which demand consideration and study. Anemia caused by a deficiency of copper may exist in an infant given an unsupplemented milk diet throughout the first year of life. In an adult on a highly restricted milk diet, such as the milk diet for gastric or duodenal ulcer maintained for a long period of time, such a condition may likewise ensue. Furthermore, just as hyperglycemia in diabetes does not denote an increased utilization of carbohydrate, so hypercupremia may not necessarily indicate an increased utilization of copper. Failure of the bone marrow or liver to employ the copper or a reduced elimination of copper from the body may be responsible for the higher copper level. Anemia may be associated with, or in some cases may be the result of, a disturbance in the copper metabolism.

It seems that hypercupremia represents a response to an emergency and that the mobilization of copper is effected to combat the anemia. We recognize the significant part that copper plays in hematopoiesis, but we postulate that in man, at least, sufficient copper is stored and made available during emergencies to minimize the possible occurrence of anemia caused by a deficiency of copper. We are continuing with a study of this problem.

SUMMARY

We have designated an increase in the copper content of the blood as hypercupremia and a decrease in the copper content of the blood as hypocupremia. An increased copper concentration, or hypercupremia, was observed in various conditions with abnormal blood pictures, such as secondary anemia, pernicious anemia, von Jaksch's anemia, sickle cell anemia, Banti's disease, malaria, myelogenous leukemia, arsenic poisoning and carcinoma.

An inverse relationship exists between the copper and the iron content of the blood in anemia. As the iron content falls the copper content tends to rise. Hypercupremia is the usual response to hypoferronemia.

The inverse relationship of copper and iron in anemia is clearly illustrated in a case of polycythaemia vera. When first examined the patient's blood iron content was extraordinarily high, while the copper content was normal. Treatment with phenylhydrazine resulted in temporary anemia. The low iron content was associated with hypercupremia. When the administration of phenylhydrazine was discon-

tinued, and liver and iron therapy was instituted, the iron content rose and the copper content fell.

Tuberculosis is also characterized by hypercupremia. The average copper content of the blood of ten men with tuberculosis was 0.182 mg. per hundred cubic centimeters, and that of ten women with tuberculosis was 0.195 mg.

The hypercupremia of tuberculosis most likely coincides with the inverse relationship of copper and iron in the blood which obtains in anemia. The anemia which is often found in tuberculosis is probably the factor most responsible for the increased copper level of the blood.

That copper plays a significant rôle in hematopoiesis is suggested by its increase in the blood stream in almost all anemic states. Our figures indicate that the majority of patients with anemia, regardless of its chronicity or severity, show hypercupremia. It is evident, therefore, that sufficient quantities are stored for and made available in emergencies. This fact minimizes the possibility of the occurrence of anemia caused by the deficiency of copper in man.

III. BLOOD COPPER AND IRON IN PREGNANCY AND IN THE NEW-BORN

We made determinations of the copper and the iron content of the blood of twenty-five pregnant women in various months of gestation. The findings are presented in table 9. The blood copper of the average parturient, which was 0.195 mg. per hundred cubic centimeters, represents a 50 per cent increase over the figure (0.131 mg.) which we reported as the average copper content for fifty normal women who were not pregnant. Taking into consideration the increase in the blood volume in pregnancy, which at term reaches the extent of 23 per cent in the average case,[48] the total amount of copper in the blood stream in pregnancy is actually about twice the amount present in the nongravid state. Instead of the 6 mg. of copper present in the entire volume of blood of the average woman, as much as 12 mg. may be found in the blood of the pregnant woman.

The average iron content of the blood for the series of pregnant women, which was 40.44 mg. per hundred cubic centimeters, was below the figure (45 mg.) which we reported as the mode for 100 normal women, and therefore represents anemia, while the average copper content (0.195 mg.) was above the average for normal women and represents hypercupremia. On examining individual subjects, however, we found two significant types of blood picture in pregnancy. In one type, a normal iron content, or one slightly below normal, was accom-

48. Dieckman, W. J., and Wegner, C. R.: The Blood in Normal Pregnancy: I. Blood and Plasma Volumes, Arch. Int. Med. **53**:71 (Jan.) 1934.

panied by a high copper content. Patients 1, 4, 7, 8, 13, 18, 20 and 25 presented such a picture. The high copper level despite the normal iron level may be explained by the fact that the maternal blood transports copper to the fetus. The fetal liver has been found to contain from six to ten times as much copper per kilogram of weight as does the adult human liver. Sheldon [49] stated that 7 mg. of copper is stored in the liver of a new-born infant.

In the second type of blood picture we found true anemia. In this type a low iron content was associated with a high copper content. To

TABLE 9.—*Values for Copper and Iron in the Blood of Twenty-Five Pregnant Women*

Name	Month	Red Blood Cells	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Iron Index	Iron Color Index
1. Sml.	6	4,400,000	0.147	43.35	12.94	9.85	0.99
2. Han.	5	3,500,000	0.186	34.85	10.40	9.96	1.00
3. Bal.	7	3,750,000	0.212	29.95	8.94	7.99	0.80
4. Kom.	5	4,560,000	0.221	43.65	13.03	9.59	0.96
5. Sta.	7	4,450,000	0.256	38.90	11.61	8.74	0.87
6. Ful.	5	4,000,000	0.178	42.35	12.64	10.57	1.06
7. Gre.	5	3,900,000	0.215	43.45	12.97	11.14	1.11
8. Wei.	6	4,200,000	0.212	44.25	13.21	10.54	1.05
9. Suc.	9	4,500,000	0.197	41.30	12.33	9.18	0.92
10. McI.	5	3,500,000	0.188	36.20	10.81	10.34	1.03
11. Mal.	9	4,400,000	0.175	42.20	12.60	9.59	0.96
12. Wat.	9	4,150,000	0.269	38.45	11.48	9.27	0.93
13. Obe.	9	4,400,000	0.147	45.45	13.57	10.33	1.03
14. Sme.	5	4,150,000	0.195	39.20	11.70	9.45	0.95
15. Boy.	5	4,350,000	0.208	43.45	12.97	9.99	1.00
16. Hol.	9	3,350,000	0.172	37.30	11.13	11.13	1.11
17. Unt.	6	3,700,000	0.216	36.50	10.90	9.87	0.99
18. Var.	5	4,200,000	0.167	43.10	12.87	10.26	1.03
19. Jac.	7	3,950,000	0.250	39.85	11.90	10.09	1.01
20. Thl.	9	3,950,000	0.200	42.90	12.81	10.86	1.09
21. Wil.	5	3,950,000	0.180	42.90	12.81	10.86	1.09
22. McA.	8	4,000,000	0.138	41.00	12.24	10.25	1.03
23. Cen.	5	3,300,000	0.153	37.05	11.06	11.23	1.12
24. Bag.	5	4,000,000	0.212	40.00	11.94	10.00	1.00
25. Chr.	8	3,800,000	0.177	43.45	12.97	11.43	1.14
Average		4,016,000	0.195	40.44	12.07	10.10	1.01

cite an example, patient 3 had a red cell count of 3,500,000, an iron content of 29.95 mg. and a copper content of 0.212 mg. per hundred cubic centimeters. The figures for patients 2, 5, 10, 12, 14, 16, 17 and 23 illustrate this type. The hypercupremia of pregnancy may therefore be more than the result of the transfer of comparatively large quantities of copper from the maternal blood to the fetus. In the event of anemia complicating pregnancy it may also represent an effort on the part of the mother to mobilize a hematopoietic stimulant. Such a mobilization of copper coincides with the hypercupremia which we found in anemias other than that of pregnancy. The pregnant women in our series were patients who presented themselves at the clinic for antepartum care. Despite the fact that the determinations on the blood were

49. Sheldon, J. H.: Some Considerations on the Influence of Copper and Manganese on the Therapeutic Activity of Iron, Brit. M. J. **2**:869 (Nov. 12) 1932.

made during the hot months of July and August, when dehydration reduces the plasma volume and the iron content of the blood tends to increase, the average blood iron content of these women was below par. This so-called physiologic anemia of pregnancy occurs in a high percentage of patients in the clinic.

Other investigators also have determined the blood copper in pregnancy. Their results are based either on too small a group or on determinations on the blood serum instead of on whole blood. Krebs [50] reported a series of determinations of copper on the blood serum of nineteen pregnant women. His average finding for the group indicated that the serum copper was twice as high during pregnancy as in the nongravid state. Gorter, Grendel and Weyers [41] reported an increased copper level in the blood of seven pregnant women. Sheldon and Ramage,[40] using a spectroscopic method, observed a strong copper line in a case of severe anemia of pregnancy. Locke, Main and Robash [42] reported a high copper level in the serum of four pregnant women.

COMPARISON OF FETAL AND MATERNAL BLOOD

We have examined and compared the blood of the new-born, taken from the umbilical cord, with the maternal blood drawn immediately before delivery. The following interesting results were obtained.

Specimens of Blood	Copper, Mg. per 100 Cc.	Iron, Mg. per 100 Cc.
1. Maternal	0.183	42.00
Fetal (male)	0.076	53.45
2. Maternal	0.230	39.85
Fetal (male)	0.071	43.65
3. Maternal	0.298	43.10
Fetal (female)	0.075	50.20
4. Maternal	0.194	38.30
Fetal (female)	0.098	50.00
5. Maternal	0.189	34.50
Fetal (male)	0.089	54.65

In this series the average copper content of the maternal blood, which was 0.219 mg. per hundred cubic centimeters, is characteristic of the hypercupremia of pregnancy. The average copper content of the new-born, which was 0.082 mg. per hundred cubic centimeters, represents a comparatively low level. In case 3 the maternal blood was four times as rich in copper as was the fetal blood. Moreover, the figures for cases 1, 2 and 3 indicate that the new-born infants possessed, per unit volume of blood, only a little more than half of the copper found in the average normal adult.

On receiving the copper which is diffused through the placenta, the fetus does not retain the bulk of the element in the blood stream but evidently stores it in the liver. The fact that the liver and the spleen

50. Krebs, H. A.: Ueber das Kupfer im menschlichen Blutserum, Klin. Wchnschr. **7**:584, 1928.

serve as the reservoirs for the greater portion of the copper in the fetus may be associated with the importance of these organs as hematopoietic centers in the embryo. In the normal adult the manufacture of erythrocytes is exclusively the function of the bone marrow. If it is true that copper performs its biologic function chiefly in the bone marrow by stimulating the formation of hemoglobin and the maturation of erythrocytes, the blood of the adult should be relatively rich in this element. The sinusoids of the bone marrow in which the red cells are manufactured are part of the closed circulatory system, and a high level of copper in the blood would therefore be necessary to maintain a sufficient supply for these erythropoietic centers. These facts serve to explain the differences between the blood copper of the fetus and that of the normal adult.

The polycythemia of the new-born accounts for the high iron content of the blood drawn from the umbilical cord. The average iron content of the fetal blood in the five cases was 50.39 mg., compared with 39.55 mg. in the maternal blood. The relatively high level of iron in the blood is maintained in the fetus, as in case 5 (54.65 mg.), even when the maternal blood (34.5 mg.) shows definite anemia.

SUMMARY

We have made determinations of the copper content of the whole blood of twenty-five pregnant women. The average for the series, which was 0.195 mg. per hundred cubic centimeters, represents a 50 per cent increase over the average (0.131 mg.) for fifty normal women who were not pregnant. Hypercupremia seems to be a constant finding in pregnancy.

If one takes into consideration the increase in blood volume in pregnancy, which in the average case occurs to the extent of 23 per cent, the total amount of copper present in the blood stream of the parturient woman is twice the amount present in the blood stream of the normal woman who is not pregnant.

Determinations were made of the iron content of the whole blood of the twenty-five pregnant women. The average value, which was 40.44 mg. per hundred cubic centimeters, is below the figure (45 mg.) which we have established as the mode for one hundred normal women who were not pregnant. Relative anemia usually accompanies pregnancy.

Hypercupremia of pregnancy, when associated with a normal iron content, is physiologic and reflects the normal mechanism of transporting copper from the maternal blood to the fetal reservoirs. Hypercupremia of pregnancy, when accompanied by hypoferronemia, may represent not only this mechanism but also mobilization of copper to combat the anemia which is commonly found in the pregnant state.

A comparison of the blood of the new-born and that of the mother was made in five cases. The maternal blood was from two to four times as rich in copper as was the blood of the umbilical cord, whereas the iron content of the blood of the new-born infant was always at a higher level than was the iron content of the blood of the mother.

A relatively high iron content may be maintained in the blood of the fetus even when the maternal blood shows definite hypoferronemia.

The copper content of the blood of the umbilical cord, which averaged 0.082 mg. per hundred cubic centimeters, was only a little more than one-half as high as that of the average normal adult.

In the normal adult hematopoiesis is the exclusive function of the bone marrow, and the blood copper is maintained at a relatively high level to supply the sinusoids, which are in direct communication with the blood stream, with the hematopoietic stimulant. In the fetus, since the liver and the spleen are centers for hematopoiesis, there is probably a mobilization of copper in these organs instead of in the blood.

REACTION (p_H) AND CARBON DIOXIDE CONTENT OF THE VENOUS PLASMA IN PERNICIOUS ANEMIA

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That there is a distinct interrelationship between the gastric secretory mechanism and the acid-base balance of the blood has been definitely shown in the literature (Hermanns and Sakr,[1] Bakaltschuk,[2] Apperly and Crabtree,[3] Browne and Vineberg [4] and others). Hermanns and Sakr, who studied patients in whom the secretion was abnormal, reported that gastric hyperacidity is characterized by a low alkali reserve of the blood and achylia by a high reserve.

Studies of the acid-base balance that have been conducted on patients with pernicious anemia, in whom there is a complete dysfunction of the gastric glands, without exception have indicated abnormalities in the alkali reserve or in the reaction of the blood associated with this disease. Kahn and Barsky [5] (1919), Gettler and Lindeman [6] (1920) and Ashby [7] (1925) reported a lowered alkali reserve in the majority of the cases studied, indicating acidosis, whereas, on the other hand, Barr and Peters [8] (1921), Dautrebande [9] (1925), Dill and his

From the Lilly Laboratory for Clinical Research of the Indianapolis City Hospital.

1. Hermanns, L., and Sakr, J. M.: Ueber die Regulierung des Säurebasengleichgewichtes bei den Sekretionsstörungen des Magens, Klin. Wchnschr. **6**:1367 (July 16) 1927.

2. Bakaltschuk, M.: Der Magen als Mitregulator des Säurebasengleichgewichts, Klin. Wchnschr. **7**:1551 (Aug. 12) 1928.

3. Apperly, F. L., and Crabtree, M. G.: The Relation of Gastric Function to the Chemical Composition of the Blood, J. Physiol. **73**:331 (Dec.) 1931.

4. Browne, J. S. L., and Vineberg, A. M.: The Interdependence of Gastric Secretion and the CO_2 Content of the Blood, J. Physiol. **75**:345 (July) 1932.

5. Kahn, M., and Barsky, J.: Studies of the Chemistry of Pernicious Anemia, Arch. Int. Med. **23**:334 (March) 1919.

6. Gettler, A. O., and Lindeman, Edward: Blood Chemistry of Pernicious Anemia, Arch. Int. Med. **26**:453 (Oct.) 1920.

7. Ashby, W.: Blood Volume: VI. The Relationship Between Blood Volume, Total Corpuscle Content and Alkaline Reserve in Cases of Pernicious Anemia, Arch. Int. Med. **36**:24 (July) 1925.

8. Barr, D. P., and Peters, J. P., Jr.: III. The Carbon Dioxide Absorption Curve and Carbon Dioxide Tension of the Blood in Severe Anemia, J. Biol. Chem. **45**:571 (Feb.) 1921.

9. Dautrebande, L.: L'alcalose paradoxale de l'anémie pernicieuse, Compt. rend. Soc. de biol. **93**:1031 (Oct. 30) 1925.

co-workers [10] (1928) and Hitzenberger and Tuchfeld [11] (1931), largely on the basis of experimentally derived curves of the carbon dioxide absorption, postulated the existence of alkalosis in this disease.

With the hope of throwing more light on this phase of pernicious anemia, twenty-nine patients with typical pernicious anemia have been studied relative to the hydrogen ion concentration and the carbon dioxide content of the venous blood, and the data have been compared with those obtained from a series of sixteen normal subjects.

The patients with pernicious anemia were grouped according to the red blood cell counts and according to the degree of involvement of the central nervous system. Since alkalosis in itself is known to be capable of producing paresthesia in diseases other than pernicious anemia, an attempt has been made to correlate the possible relationship between the acid-base equilibrium in pernicious anemia and the clinical manifestations of involvement of the central nervous system.

Weiss, Kiss and Kuszing,[12] in a paper relating to the reaction of the blood and to hemopoiesis, suggested that the clinical improvement following the administration of hydrochloric acid might be due in some degree to the lowering of the p_H of the blood. In order to note any appreciable changes in the acid-base equilibrium of the blood we determined the p_H and the carbon dioxide content of the venous blood in a series of patients with pernicious anemia before and after the daily administration by mouth of from 6 to 10 cc. of a dilute solution (10 per cent) of hydrochloric acid.

PROCEDURE AND METHODS

The blood was drawn in each case from a large vein of the arm, after stasis of less than one minute, into an oiled syringe and introduced under oil into a centrifuge tube coated with a sufficient amount of potassium oxalate to yield a concentration of 3 mg. of oxalate per cubic centimeter of blood. Following replacement of the layer of oil by paraffin of a low melting point, the blood was immediately centrifugated; the separated plasma, sampled through a hole bored under oil through the paraffin, was promptly analyzed for the p_H and the carbon dioxide content. The p_H was determined according to Hastings and Sendroy's [13] bicolor

10. Dill, D. B.; Bock, A. V.; van Caulaert, C.; Fölling, A.: Hurxthal, L. M., and Henderson, L. J.: Blood as a Physiochemical System: VII. The Composition and Respiratory Exchanges of Human Blood During Recovery from Pernicious Anemia, J. Biol. Chem. **78**:191 (June) 1928.

11. Hitzenberger, K., and Tuchfeld, F.: Die Blutreaktron der perniziösen Anämie im schlechten und guten Zustand, Ztschr. f. klin. Med. **117**:607, 1931.

12. Weiss, S.; Kiss, F., and Kuszing, N.: Ueber den Einfluss der Wasserstoffionenkonzentration des Blutes auf die Zahl der roten Blutkörperchen, Ztschr. f. d. ges. exper. Med. **60**:58, 1928.

13. Hastings, A. B., and Sendroy, J., Jr.: Studies of Acidosis: XX. The Colorimetric Determination of Blood p_H at Body Temperature Without Buffer Standards, J. Biol. Chem. **61**:695 (Oct.) 1924.

modification of Cullen's method; the manometric method of Van Slyke and Neill [14] was employed in the determination of the carbon dioxide content. From the p_H and the carbon dioxide content of the plasma, the carbon dioxide tension was calculated graphically by means of the line chart of Van Slyke and Sendroy.[15]

All samples of blood were drawn between the hours of 9 and 11 a. m. Experiments confirming the reports of Cullen and Earle [16] were performed, indicating that the effect of breakfast was a negligible factor, so that we felt justified in assuming that the values obtained in each case represented basal conditions. All analyses were performed during July and August.

RESULTS

Normal Subjects.—In table 1 are presented the results of the analyses of the venous plasma obtained from sixteen normal persons.

TABLE 1.—*The p_H, Carbon Dioxide Content and Carbon Dioxide Tension of the Venous Plasma in Sixteen Normal Subjects*

Subject	Age, Years	Sex	p_H	Carbon Dioxide Content, Volumes per Cent	Carbon Dioxide Tension, Mm.
1	22	M	7.37	66.5	50.0
2	23	F	7.38	55.9	41.6
3	24	M	7.35	62.0	48.8
4	23	F	7.37	60.5	45.5
5	23	F	7.38	61.8	46.0
6	26	F	7.36	57.0	44.5
7	22	F	7.39	55.1	40.0
8	19	M	7.38	55.2	41.2
9	33	M	7.37	61.4	46.4
10	21	M	7.34	67.1	54.0
11	23	M	7.37	66.8	51.0
12	24	M	7.34	64.9	52.8
13	21	F	7.37	55.9	42.0
14	22	F	7.38	61.6	45.8
15	36	M	7.37	67.7	51.0
16	21	F	7.38	54.7	40.5
Mean value			7.37 ± 0.003*	61.5 ± 0.84*	46.4 ± 0.82*
Coefficient of variation			0.2	7.3	9.5

* Probable error of the mean.

The range of the p_H for the normal group was from 7.34 to 7.39. The average p_H was 7.37. Crimm and Watson [17] reported an average p_H of

14. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523 (Sept.) 1924.

15. Van Slyke, D. D., and Sendroy, J., Jr.: Studies of Gas and Electrolyte Equilibria in Blood: XV. Line Charts for Graphic Calculations by the Henderson-Hasselbalch Equation, and for Calculating Plasma Carbon Dioxide Content from Whole Blood Content, J. Biol. Chem. **79**:781 (Oct.) 1928.

16. Cullen, G. E., and Earle, I. P.: Studies of the Acid-Base Condition of Blood: II. Physiological Changes in Acid-Base Condition Throughout the Day, J. Biol. Chem. **83**:545 (Sept.) 1929.

17. Crimm, P. D., and Watson, H. L.: Vitamin Therapy in Pulmonary Tuberculosis: IV. Comparison of the H-Ion Concentration of the Blood in Tuberculosis with Normals on the Same Dietary, Ann. Int. Med. **7**:109 (July) 1933.

7.37 for fifty normal persons and Woodward and her co-workers,[18] an average value of 7.38 for twenty-five normal subjects.

The carbon dioxide content ranged from 54.7 to 67.7 volumes per cent, the mean approximating 61.5 volumes per cent. Earle and Cullen [19] reported the normal range of the total carbon dioxide content of the venous plasma to lie between 55 and 74 volumes per cent.

The calculated carbon dioxide tension varied in this group of normal subjects from 40.5 to 54 mm., averaging approximately

TABLE 2.—*The p_H, Carbon Dioxide Content and Carbon Dioxide Tension of the Venous Plasma in Twenty-Nine Patients with Pernicious Anemia*

Patient	Age, Years	Sex	Red Blood Cells, Millions per C.Mm.	Hemoglobin, per Cent*	Involvement of Central Nervous System	p_H	Carbon Dioxide Content, Volumes per Cent	Carbon Dioxide Tension, Mm.
1	74	M	4.50	94.3	Advanced	7.34	57.8	46.5
2	39	F	1.67	32.7	None	7.47	58.8	36.0
3	55	M	2.90	63.7	Moderate	7.30	56.8	50.0
4	65	M	4.90	98.3	None	7.43	53.3	35.7
5	41	F	4.93	90.5	Early	7.38	57.0	42.3
6	46	M	5.28	85.0	Early	7.41	58.9	40.5
7	57	M	5.52	86.0	Advanced	7.38	55.6	41.5
8	66	M	5.05	83.0	Advanced	7.39	58.3	42.5
9	56	M	4.69	78.2	None	7.39	59.5	43.0
10	63	F	5.64	95.6	Early	7.37	60.8	46.0
11	57	M	3.33	60.2	Advanced	7.41	60.8	41.8
12	64	M	4.64	84.0	Advanced	7.39	60.0	43.3
13	55	F	5.30	78.2	Advanced	7.37	61.9	46.5
14	38	F	4.04	69.5	Early	7.39	54.4	39.8
15	57	M	4.15	67.4	Early	7.40	56.8	40.0
16	48	M	4.95	87.1	Advanced	7.38	59.9	44.2
17	59	F	5.03	70.2	Early	7.37	57.1	43.0
18	63	M	5.67	109.4	Moderate	7.36	61.8	47.8
19	54	M	2.85	47.1	Moderate	7.37	57.2	43.0
20	63	F	3.76	34.6	Moderate	7.37	53.3	40.0
21	58	M	4.09	78.2	Advanced	7.36	57.6	42.8
22	47	F	3.98	70.2	Advanced	7.36	49.4	38.2
23	43	M	4.50	68.8	Early	7.39	59.1	42.8
24	51	F	4.58	68.8	Moderate	7.38	63.4	47.0
25	55	M	4.79	94.3	Advanced	7.37	63.3	47.8
26	65	F	2.00	53.5	Moderate	7.39	63.0	46.2
27	63	M	2.14	43.0	Early	7.39	65.8	47.7
28	56	M	2.38	47.1	Moderate	7.37	62.3	47.0
29	39	F	1.87	40.0	None	7.41	56.4	39.0
Mean values						7.38 ± 0.005†	59.0 ± 0.5	44.6 ± 0.5
Coefficient of variation						0.54	6.3	8.7

* Determined by Newcomer's method.
† Probable error of the means.

46.4 mm. From the data of Earle and Cullen the normal carbon dioxide tension of the venous plasma was found to vary from 37 to 58 mm.

18. Woodward, G. E.; Schoonover, J. W.; Fry, E. G.; Torrance, E. G., and McDonald, E.: The Hydrogen-Ion Concentration of the Blood in Untreated Cancer Cases and Its Relation to Prognosis, J. Lab. & Clin. Med. **16**:704 (April) 1931.

19. Earle, I. P., and Cullen, G. E.: Studies of the Acid-Base Condition of Blood: I. Normal Variation in p_H and CO_2 Content of Blood Sera, J. Biol. Chem. **83**:539 (Sept.) 1929.

Subjects with Pernicious Anemia.—In table 2 are listed the results of the determinations of the p_H and the carbon dioxide content of the venous plasma in twenty-nine patients with pernicious anemia. Each of the patients was known to possess true achylia, and none had received hydrochloric acid for at least seven days prior to the analysis.

TABLE 3.—*The Mean p_H, Carbon Dioxide Content and Carbon Dioxide Tension of the Venous Plasma in Normal Subjects and in Various Groups of Patients with Pernicious Anemia, Divided According to Severity of Clinical Symptoms and to Treatment with Hydrochloric Acid*

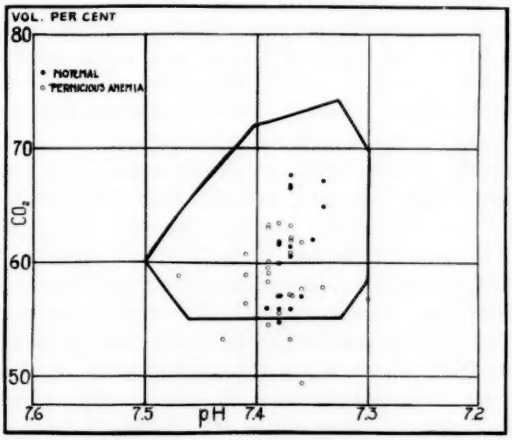
	Number of Subjects	p_H		Carbon Dioxide Content, Vols. per Cent		Carbon Dioxide Tension, Mm.	
		Mean Value	Coefficient of Variation	Mean Value	Coefficient of Variation	Mean Value	Coefficient of Variation
I. Normal subjects.....	16	7.37 ± 0.003*	0.2	61.5 ± 0.84	7.3	46.4 ± 0.82	9.5
II. Patients with pernicious anemia							
A. With early or no demonstrable involvement of the central nervous system.....	12	7.40 ± 0.005	0.4	58.2 ± 0.57	5.0	41.3 ± 0.68	8.3
B. With from moderate to advanced involvement of the central nervous system.....	17	7.37 ± 0.004	0.3	58.9 ± 0.72	6.3	44.5 ± 0.61	7.0
C. With red blood cell counts above 3,000,000.....	22	7.38 ± 0.003	0.3	58.4 ± 0.49	5.8	42.9 ± 0.45	7.2
D. With red blood cell counts below 3,000,000.....	7	7.39 ± 0.012	0.6	60.0 ± 0.77	5.0	44.1 ± 1.21	10.7
E. Receiving from 6 to 10 cc. of 10 per cent hydrochloric acid daily.....	5	7.39 ± 0.027	1.2	57.4 ± 1.1	6.4	40.8 ± 0.86	7.0
F. Patients in group E after one week's suspension of treatment with 10 per cent hydrochloric acid.....	5	7.37 ± 0.003	0.2	59.8 ± 0.74	4.0	44.4 ± 0.58	4.2
G. All patients.....	29	7.38 ± 0.005	0.5	59.0 ± 0.5	6.3	44.6 ± 0.5	8.7

* Probable error of the mean.

The range of the p_H in this group was from 7.30 to 7.47, the mean value approximating 7.38. The total carbon dioxide content of the venous plasma varied between 53.3 and 65.8 volumes per cent, averaging approximately 59 volumes per cent. The calculated carbon dioxide tension was found to lie between 35.7 and 47.8 mm., with a mean value of approximately 44.6 mm.

In table 3 are recorded the mean values for the p_H and for the carbon dioxide content of the patients with pernicious anemia, grouped according to the hematologic and the neurologic status of the patient at the time of the analysis. There are included in this table the results obtained with a series of patients who had received daily from 6 to 10 cc. of a 10 per cent solution of hydrochloric acid orally and the mean values for the same patients following suspension of the treatment for one week.

The data recorded in tables 1 and 2 are plotted in the chart, and the relation of the plotted points to the normal area published by Austin and Cullen [20] is shown.



Data recorded in tables 1 and 2 plotted according to the normal area of Austin and Cullen.[20] In the diagram, solid dots represent values for normal subjects; hollow dots, those for patients with pernicious anemia.

COMMENT

It is evident that there was no sharp variation from the normal acid-base equilibrium in the great majority of patients with pernicious anemia studied. This fact is clearly shown in the chart, in which the data for the normal subjects and for the patients with anemia are plotted together. However, it may be pointed out that there is an apparent tendency toward a deficit of alkali in pernicious anemia if the carbon dioxide content of the venous plasma is accepted as a com-

20. Austin, J. H., and Cullen, G. E.: Hydrogen-Ion Concentration of the Blood in Health and Disease, Medicine **4**:275 (Aug.) 1925.

parative measure of the alkali reserve. All of the subjects evidencing a markedly diminished carbon dioxide content are seen to be patients with pernicious anemia. In spite of this tendency, there was found no true acidosis in the sense of a decreased hydrogen ion concentration of the blood. Indeed, in a large number of the patients with pernicious anemia the blood was found to possess a slightly alkaline reaction as compared to that of the group of normal subjects.

No generalizations can justly be made in regard to either the reaction of the blood or the alkali reserve in pernicious anemia on the basis of this investigation, as is clear from a study of the mean values. The differences between the mean p_H, the total carbon dioxide content and the carbon dioxide tension of the plasma in the normal subjects and the values in the patients with pernicious anemia were, as a group, too slight to be significant. It is interesting to note, however, that the variation in the p_H was more than twice as great among the patients with pernicious anemia as among the normal subjects, whereas the variations in the carbon dioxide content and the carbon dioxide tension were approximately the same in the two groups.

Grouping the patients with pernicious anemia according to the clinical status yielded interesting results. These data are presented in table 3. It is seen that in the patients with early or no demonstrable changes in the cord, the reaction of the blood, as expressed by the p_H, was 0.03 units higher, on an average, and the carbon dioxide tension slightly lower, than in the patients with from a moderate to an advanced degree of involvement of the central nervous system. It may be said, then, that alkalosis is not a significant factor in the occurrence of paresthesias in pernicious anemia. No notable differences are to be found due to, or accompanying, the changes in the red blood cell count. Since no appreciable changes were found in the p_H or the carbon dioxide content of the venous blood following the administration of the specified amount of hydrochloric acid, it cannot be said that the therapeutic value of its administration, such as the relief of gastrointestinal symptoms, is attributable to changes in the acid-base equilibrium.

SUMMARY

The p_H and the carbon dioxide content of the venous plasma were determined in twenty-nine patients with pernicious anemia and in sixteen normal persons.

The results suggest that the condition of the acid-base equilibrium in pernicious anemia is independent of the clinical status and is essentially normal, although there is an apparent tendency toward alkalosis and a deficit of alkali.

Of possible significance is the variation of the p_H over a range which was twice as broad in the patients with pernicious anemia as in the series of normal subjects.

The daily administration of from 6 to 10 cc. of a 10 per cent solution of hydrochloric acid produced no appreciable changes in the acid-base equilibrium of the blood in the patients with pernicious anemia.

DIETS LOW IN CALORIES CONTAINING VARYING AMOUNTS OF PROTEIN

THEIR EFFECT ON LOSS IN WEIGHT AND ON THE METABOLIC RATE IN OBESE PATIENTS

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AND
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In a previous communication,[1] were reported the results of studies of nitrogen excretion in obese patients on diets low in calories, containing varying amounts of protein. It was noted that a negative nitrogen balance was unusual in patients on diets containing 90 Gm. of protein, and that the loss of nitrogen on an intake of from 13 to 14 Gm. of protein was not significant. The general conclusion reached was that the fat constitutes a mobile supply of energy which is so easily requisitioned that starvation sequelae do not develop, provided carbohydrate is furnished for antiketogenesis and protein for the "wear and tear quota."

In this paper a study of the effect of such diets on the rate of loss in weight and on the metabolic rate is reported. The periods of observation were sufficient to obviate minor variations in weight due to water retention, and thus to establish any variation observed as significant.

METHODS

The management of the experiment has been previously described. The patients were weighed each morning under standard conditions. The metabolic rate was determined once a week by the oxygen consumption method, using a McKesson machine.

RESULTS

Loss of Weight.—The great stumbling-block in the studies of reduction in weight in the obese has been the absence of an accurate measure of the energy expended and the consequent inability to set up a balance sheet covering the exchange of energy. Benedict and Root [2] have shown

From the Department of Medicine of the University of Illinois College of Medicine.

1. Keeton, Robert W., and Bone, Dorothy D.: Excretion of Nitrogen by Obese Patients on Diets Low in Calories, Containing Varying Amounts of Protein, Arch. Int. Med. **51**:890 (June) 1933.

2. Benedict, F. G., and Root, H. F.: Insensible Perspiration: Its Relations to Human Physiology and Pathology, Arch. Int. Med. **38**:1 (July) 1926.

that the basal metabolic rate may be estimated from the insensible perspiration. Newburgh and Johnston [3] extended this method to the measurement of the total production of heat by establishing precautions to avoid undue cooling of the body, sweating and the performance of work. Using this method, they concluded that loss of weight can be accurately predicted, and that the obese patient subjected to a diet inadequate in calories loses weight quantitatively.

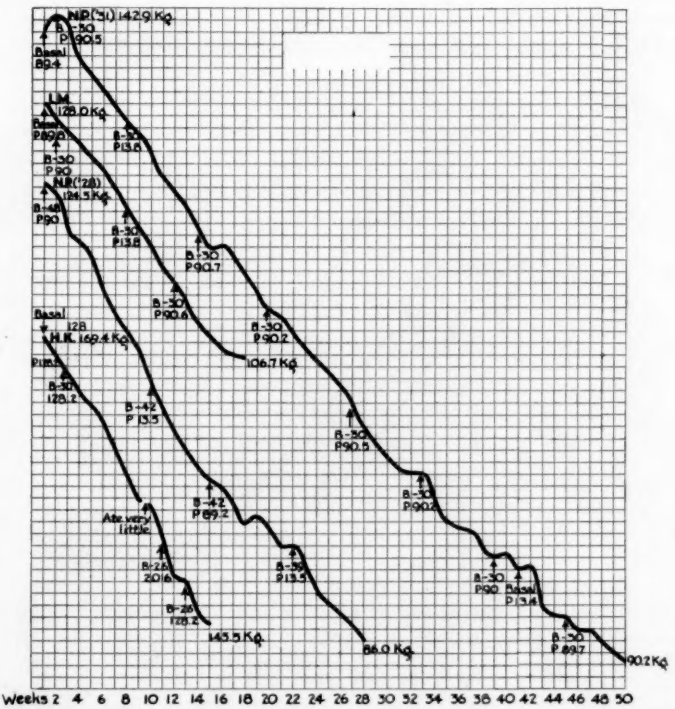

Chart 1.—Curves showing loss of weight, expressed in kilograms, during a period of several weeks, in four obese patients receiving diets low in calories containing shifting amounts of proteins varying approximately from 90 to 13 Gm. and vice versa. Each division along the ordinate represents 1 Kg.

Our patients were confined to the hospital but were allowed to be out of bed and around the wards. They usually took a period of rest in the afternoon. The activity was classified as "ambulatory." However, there were individual differences in the activity, large in some

3. Johnston, Margaret W., and Newburgh, L. H.: Determination of Total Heat Eliminated by Human Being, J. Clin. Investigation **8**:147, 1930. Newburgh, L. H., and Johnston, Margaret W.: The Nature of Obesity, ibid. **8**:197, 1930.

cases, so that the expenditure of energy in one patient could not be compared with that in another. It is to be noted that the diets are designated as "basal minus 30 per cent" or "basal minus 48 per cent." The basal requirements are based on the observed surface area rather than on the ideal surface area, as suggested by Strang and Evans.[4] Since the fat is to be regarded as storage material and is presumably not a part of the active metabolizing tissues, they thought it justifiable to discount its effect on the metabolism. However, the fat does increase the surface area, and it has been generally accepted that the metabolism varies with the surface area. A mathematical convention, therefore,

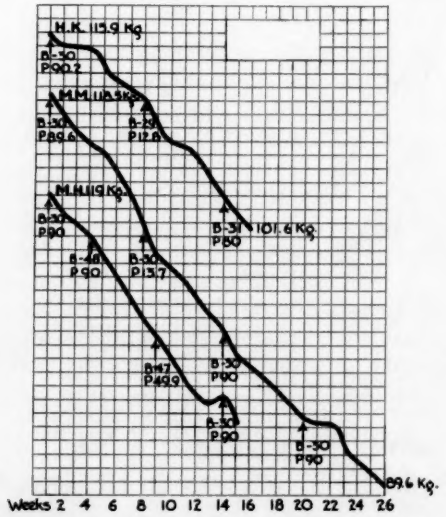

Chart 2.—Curves showing loss of weight in three obese subjects under conditions similar to those indicated in chart 1. Each division along the ordinate represents 1 Kg.

which ignores this increment in surface area due to fat does not at present seem justified.

In charts 1, 2 and 3, the weights of the patients are plotted at weekly intervals. The base line has been shifted so as to group the weight curves for comparison. Each division along the ordinate represents 1 Kg., and each division along the abscissa one week. The caloric value of the diet and the quantity of protein expressed in grams are also indicated.

In five of the experiments (NP, 1931 and LM, chart 1; HK and MM, chart 2, and SC, chart 3), the diets consisted of basal minus 30

4. Strang, James M., and Evans, Frank A.: The Energy Exchange in Obesity, J. Clin. Investigation **6**:277, 1928.

per cent calories. In the two remaining experiments (NP, 1928, chart 1, and MH, chart 2), the reduction in calories was somewhat greater, but the experimental periods are comparable. With each change of diet, the basal requirement was recalculated and adjusted to the new surface area, but there were no further adjustments during the period. It was believed that this plan subjected the patient continuously to the same quantitative degree of undernutrition and allowed any effect arising from the shifting of the protein to manifest itself.

It is to be noted that the slopes of the weight curve do not change significantly when the quantity of protein is shifted from 90 to 13 Gm., or vice versa.

The same result is shown when the data are treated differently, as in the table. Here the daily loss in weight expressed in grams is computed for each type of diet. If the loss appeared greater on the high protein diet, it is charted in the last column as H.P.; if greater on the low protein diet, as L.P. By reference to this column, it is seen that

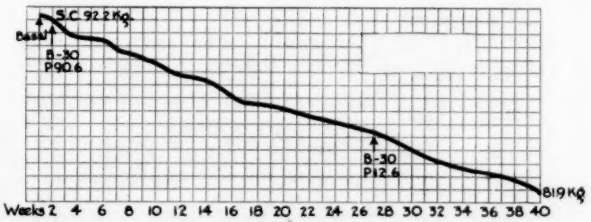

Chart 3.—Curve showing loss of weight in one obese patient under conditions similar to those indicated in charts 1 and 2. Each division along the ordinate represents 1 Kg.

in two of the patients, the loss was greater on a high protein diet, and in four, on a low protein diet; in two patients the loss was the same on the two diets, and for one the results were inconclusive. In other words, there is no correlation in the data with reference to changes in the amount of protein.

Similar observations have been previously reported in the case of hogs [5] placed on submaintenance diets with varying amounts of protein. The loss in weight paralleled the reduction in calories and was independent of changes in the protein content of the diet.

It is also to be noted that with the same proportionate reduction in the diet, the loss in weight seemed to be greater in the more obese patients. The explanation of this loss is not clear, and this conclusion

5. Keeton, Robert W.; MacKenzie, H.; Olson, S., and Pickens, L.: The Influence of Varying Amounts of Carbohydrate, Fat, Protein and Water on the Weight Loss of Hogs in Undernutrition, Am. J. Physiol. **97**:473 (June) 1931.

should not be stressed, because of the necessity of comparing the loss of weight in one subject with that in another in the absence of a measure of their activity.

The question naturally arises as to whether these experiments throw any light on the vexed problem of the specific dynamic action of food in the obese, a question which has led to many diverse studies and conflicting opinions.[6] Lusk[7] noted that carbohydrates and fats do not

Loss in Weight Under High and Low Protein Diets of Low Caloric Value in Nine Obese Patients

Patient	Name	Calories*	Protein	Weight Loss in Gm. per Day on		Diet Producing Greater Loss†
				High Protein Diet	Low Protein Diet	
1	S. C.	B-30% B-30% B-30%	14.5 2.11 14.5	120.0 Gm. for 34 days 105.4 Gm. for 43 days	113.6 Gm. for 42 days	Equal
2	H. H.	B-30% B-28% B-42%	14.4 14.4 2.24	120.2 Gm. for 22 days 113.6 Gm. for 29 days	70.9 Gm. for 25 days	H. P.
3	M. H.	B-30% B-48% B-42%	14.5 14.006	159.1 Gm. for 30 days 194.5 Gm. for 35 days	101.3 Gm. for 38 days	H. P.
4	H. K.	B-30% B-20%	20.46 2.016	282.8 Gm. for 45 days	470.8 Gm. for 14 days‡	L. P.
5	H. K.	B-30% B-29%	14.4 2.048	107.9 Gm. for 59 days	165.3 Gm. for 44 days	L. P.
6	N. P.	B-48% B-42%	14.4 2.016	231.3 Gm. for 72 days	285.9 Gm. for 31 days	L. P.
		B-42% B-39%	14.27 2.016	113.6 Gm. for 54 days	181.8 Gm. for 45 days	
7	N. P.	B-30% B-30% B-30%	14.48 2.201 14.512	216.4 Gm. for 42 days 129.86 Gm. for 42 days	221.8 Gm. for 42 days	Equal
8	M. M.	B-30% B-30% B-30%	14.432 2.192 14.368	200.2 Gm. for 42 days 140.7 Gm. for 42 days	183.98 Gm. for 42 days	Equal
9	L. M.	B-30% B-30% B-30%	14.51 2.201 14.5	178.6 Gm. for 42 days 135.3 Gm. for 42 days	211.03 Gm. for 28 days	L. P.

* B represents the basal calorie requirement.
† H. P. represents a high protein diet; L. P., a low protein diet.
‡ Experiment was of short duration.

6. Strous, S.; Saunders, A. D., and Wang, C. C.: Specific Dynamic Action of Food, Arch. Int. Med. **34**:573 (Oct.) 1924. Plaut, R.: Gaswechseluntersuchungen bei Feltsucht und Hypophysiserkrankungen, Deutsches Arch. f. klin. Med. **139**:285, 1922; Gaswechseluntersuchungen bei Feltsucht, ibid. **142**:266, 1923. Du Bois, E. F.; Spencer, H. J.; McClellan, W. S., and Falk, E.: The Specific Dynamic Action of Protein in the Obese, J. Clin. Investigation **7**:499, 1929. Lauter, S.: Zur Genese der Feltsucht, Deutsches Arch. f. klin. Med. **150**:315, 1926. Strang, J. M., and McClugage: The Specific Dynamic Action of Food in Abnormal States of Nutrition, Am. J. M. Sc. **182**:47, 1931. Johnston, Margaret W.: The Specific Dynamic Response to Protein of Individual Suffering from Disease of the Hypophysis, J. Clin. Investigation **11**:437, 1932.

7. Lusk, G.: The Specific Dynamic Action of Various Food Factors, Medicine **1**:311, 1922.

cause an increase in the metabolism, unless there is a plethora of molecules in excess of the immediate energy requirements. Thus in a fasting dog with a low respiratory quotient, the value of the quotient was raised to 1 by the intake of a certain number of grams of dextrose, and yet no elevation of the metabolism appeared. With a further increase in the dextrose the specific dynamic action then appeared, and the metabolism was increased. On the high protein diets these patients received between 1,000 and 1,200 calories with an intake of protein of 90 Gm., of carbohydrate, of from 80 to 90 Gm., and of fat from 30 to 50 Gm. With a lowering of the amount of protein to from 13 to 14 Gm., the carbohydrate intake reached a value of from 150 to 160 Gm. It is to be remembered that these diets were always inadequate in calories, approximately 45 per cent below the actual energy expended. One concludes, therefore, that no stimulating effect is to be expected from the carbohydrate or the fat. In the case of protein, the story seems to be different. Here the stimulating effect is due to the intermediary products of the oxidation of certain amino-acids (Lusk), and this effect seems to be superimposed on the energy requirements for work. Such a stimulation does not occur in the absence of the liver (Mann and his co-workers[8]); in fact, 85 per cent of the heat produced originates within the liver (Dock[9]).

Under the conditions of our experiments, if the intake of 90 Gm. of protein stimulated the metabolism more than that of 13 Gm., it was not reflected in the loss of weight. This seems to furnish evidence in favor of the lowering of the specific dynamic action of protein in the obese. However, in this connection it should be recalled that all of these patients were storing nitrogen on a diet containing 90 Gm. of protein, and on one containing 13 Gm. were not losing significant quantities of nitrogen. It seems justifiable to assume that such a storage represented additions to the deposit of nitrogen.

Lusk[7] showed that protein which is used for purposes of replacement did not cause a specific stimulation, and McCann[10] demonstrated that the specific dynamic action of protein was greatly reduced after a fast of eight days. In his patient the nitrogen excretion was not aug-

8. Mann, F. C.; Wilhelmj, C. M., and Bollman, J. L.: The Specific Dynamic Action of Glycocoll and Alanine with Special Reference to the Dehepatized Animal, Am. J. Physiol. **81**:496, 1927. The effect of Removal of the Liver on the Specific Dynamic Action of Amino-Acids Administered Intravenously, ibid. **87**:497, 1928.

9. Dock, William: The Relative Increase in Metabolism of the Liver and Other Tissues During Protein Metabolism in the Rat, Am. J. Physiol. **97**:117, 1931.

10. McCann, W. S.: An Observation of the Effect of a Protein Meal Given to a Man at the End of an Eight Day Fast, Proc. Soc. Exper. Biol. & Med. **17**: 173, 1920.

mented by the ingestion at a single meal of 350 Gm. of meat, the equivalent of 87.5 Gm. of protein. It is highly probable, therefore, that in our experiments the state of the subject was such that the foods given did not furnish an adequate stimulus for initiating specific dynamic action.

Metabolic Rate.—In chart 4, the metabolic rates estimated at weekly intervals are plotted. Each division in the abscissa represents a period of one week, and each division in the ordinate, a variation of 10 per cent in the metabolism. The zone of cross hatching represents a variation of 10 per cent above and below the zero line, which is usually considered the normal allowable variation.

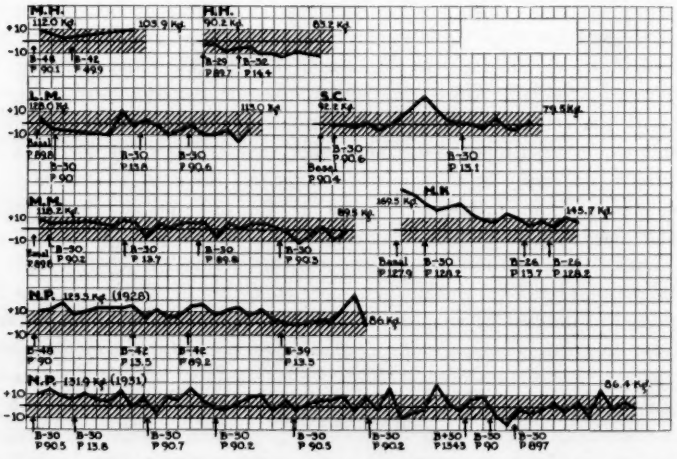

Chart 4.—Graphic representation of basal metabolic rates determined at weekly intervals over periods of from eight to fifty-three weeks for the eight obese patients whose weight curves are shown in charts 1, 2 and 3. The curves for the weekly determinations of the rate are indicated by heavy, solid lines; the limits of normal variation in the basal metabolic rate, by cross-hatched areas.

The shortest period over which metabolic rates were determined was eight weeks, in the case of M. H., a patient confined to bed. The longest period was fifty-three weeks. These periods certainly gave abundant opportunities for changes in the rate which might result from the experimental procedures to manifest themselves. It should be mentioned that H. K., a short, obese, thick-chested, apprehensive woman, had considerable difficulty in learning to cooperate in the test. On several occasions at the beginning, it was necessary to discard the test as obviously incorrect and repeat it on succeeding days. With the exception of the experiments on this patient, one may conclude that the metabolic rate

does not decrease in an obese patient undergoing reduction in weight by the restriction of the diet. It may be further observed that the metabolic rate is not decreased when, in addition to the reduction in calories, the protein in the diet is lowered so as to induce "specific nitrogen hunger" and establish the excretion of a "nitrogen minimum" in the urine.

Strang and Evans [4] obtained the same results although, as previously mentioned, their patients lost somewhat less weight. However, they preferred to estimate the metabolism on the basis of the ideal rather than the observed surface area. With this method of calculation, they concluded that the metabolism of the obese patient is above the normal and that during reduction in weight it returns to normal. According to this view, the reduction process is responsible for the lowering of the metabolism.

In the normal subject, as reported by Benedict and his associates [11] and as discussed by Lusk,[12] the metabolic rate decreases approximately 30 per cent following the sudden reduction of calories. Lusk summarized the situation as follows: "A minimal metabolic rate, which is two-thirds that of the normal basal metabolism, seems to be easy to establish and affords another of those striking 'factors of safety' of which Meltzer has so cogently written."

Anderson and Lusk [13] have made observations on the influence of a normal maintenance diet on the basal metabolism of a dog before and after fasting. They noted that after the metabolism had been reduced by fasting, a maintenance diet did not restore it to normal the following day, and they concluded that evidently the condition of the body, and not a large influx of food on the day previous, determines the height of the basal metabolism.

Deuel, Sandiford, Sandiford and Boothby [14] reported an experiment on a normal subject, H. J. D., placed on a protein-free diet of submaintenance caloric value. This subject, although labeled "normal," may have been slightly overweight (15 per cent). However, his metabolic rate fell during the experiment from —9 per cent to —20 per

11. Benedict, F. G.; Miles, W. R.; Roth, P., and Smith, H. M.: Human Vitality and Efficiency Under Prolonged Restricted Diet, Washington, D. C., Carnegie Institution of Washington, 1919, pub. 280.

12. Lusk, G.: The Physiological Effects of Undernutrition, Physiol. Rev. **1**: 523, 1921.

13. Anderson, R. J., and Lusk, G.: Animal Colorimetry: XIII. Inter-relation Between Diet and Body Condition and the Energy Production During Mechanical Work, J. Biol. Chem. **32**:421, 1917; cited by Lusk.[12]

14. Deuel, Harry J., Jr.; Sandiford, Irene; Sandiford, Kathleen, and Boothby, Walter M.: The Effect of Sixty-Three Days of a Protein-Free Diet on the Nitrogen Partition Products in the Urine and on the Heat Production, J. Biol. Chem. **76**:391, 1928.

cent. It may be suggested that this decrease in the rate was due to the absence of protein from his diet. This explanation is rendered improbable by the occurrence of a similar decrease in patients on diets containing maintenance quantities of protein. It has also been noted by Allen and Du Bois [15] that subnormal weight is associated with a lower metabolism than normal weight. Again we quote from Lusk, who stated that there is not only a mechanism for the maintenance of a minimum of nitrogen which protects life from destruction, but, in the normal person, a biologic adaptation to a lowered energy intake, which prevents the exhaustion of the reserves of body fat.

In the obese person, the large stores of fat are so readily available for energy production that the body stores of nitrogen are preserved, even when the individual is faced with specific nitrogen hunger. These stores of fat also prevent the lowering of the metabolic rate which in the normal person is produced by a shortage of calories. There is no such shortage in the obese.

CONCLUSIONS

1. Obese patients confined to the hospital, allowed the freedom of the ward and receiving diets of from basal minus 30 per cent to basal minus 48 per cent calories lose weight equally well when these diets contain 90 or 13 Gm. of protein. Such diets supply approximately 55 per cent of their actual caloric requirement. The remainder is secured from the body fat.

2. Under the conditions of the experiment there is negligible stimulation of the metabolism by the food. This experiment throws no light on the specific dynamic action of foods in the obese.

3. The metabolic rate is not lowered by a dietary undernutrition of this degree of severity lasting for from eight to fifty-three weeks.

4. The metabolic rate is not lowered by the same degree of dietary undernutrition when it is associated with specific nitrogen hunger.

5. The supplies of stored fat not only protect the body from loss of nitrogen but they also prevent the conservation of energy seen in the normal person when subjected to undernutrition.

15. Allen, F. M., and Du Bois, E. F.: Clinical Calorimetry: XVII. Metabolism and Treatment in Diabetes, Arch. Int. Med. **17**:1010 (June) 1916.

Alexander - constant anxiety state ⇒ irritation of hypothalamus ⇒ hypersecretion + motility - thru sym. N. Sys. stimn -

PEPTIC ULCER

NATURE AND TREATMENT BASED ON A STUDY OF ONE THOUSAND, FOUR HUNDRED AND THIRTY-FIVE CASES

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Peptic ulcer continues to provoke voluminous and diverse opinions each year in respect to both its nature and its treatment. No one can read more than a few of those opinions without bewilderment, and this confusion serves to perpetuate the admittedly unsatisfactory management of the condition. Only a careful and prolonged observation of many patients helps to distinguish fact from theory. We are emboldened to restate our views because time has confirmed them and because we believe that they offer the best available approach to the handling of the individual cases.

Our first report,[1] published in 1929, was a statistical survey of 556 cases of ulcer of the stomach and duodenum. For our present purpose all our cases, up to Jan. 1, 1932, including the original series, have been analyzed in the same manner. There are 1,435 cases (table 1), and wherever possible the figures are relegated to tables. We wish to discuss the problem generally rather than to substitute new figures for old.

NATURE OF THE DISEASE

The fundamental cause of peptic ulcer remains unknown in spite of an enormous amount of investigation. Experimentally it is possible to produce ulcer—at least acute ulcer—by a great number of unrelated methods, but it is not clear whether any one of these methods is the sole cause of all the chronic lesions found in man. The chief theories—vascular (Virchow), mechanical (Aschoff), constitutional (Draper), infectious (Rosenow) and neurogenic (von Bergmann)—are well known and have been reviewed recently by Rivers.[2] No one of these theories seems to fit all the instances of the disease, though various combinations of the conditions they analyze may occur.

From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Emery, E. S., Jr., and Monroe, R. T.: Peptic Ulcer: A Study of Five Hundred and Fifty-Six Cases, Arch. Int. Med. **43**:846 (June) 1929.

2. Rivers, A. B.: Clinical Consideration of the Etiology of Peptic Ulcer, Arch. Int. Med. **53**:97 (Jan.) 1934.

The Acid Factor.—Certain characteristics of the disease are universally agreed on. One of these is that it occurs only in the regions of the gastro-intestinal tract which are in contact with hydrochloric acid. Ulcer is found in the stomach, in the beginning of the duodenum, in the esophagus just above the cardiac sphincter and in the jejunum when it has been anastomosed to the stomach by some surgical procedure. Lindau [3] has pointed out that an ulcer which occurs in a Meckel's diverticulum or in the esophagus are associated with aberrant gastric tissue. Palmer's [4] studies on the clinical relationship of free hydrochloric acid to active ulcer are in entire accord with our experience. We have observed no instance in which an ulcer gave characteristic symptoms in the absence of free hydrochloric acid. Two patients, one with pernicious anemia and the other with osteitis deformans and achlorhydria, even after the administration of histamine had typical roentgenologic appearances of duodenal ulcer but did not have ulcer distress; there was no opportunity to determine whether they had true ulcers or not.

TABLE 1.—*General Survey of the Cases Reported in This Study* *

Total number of patients	1,435
Age at time of first observation	14-80 years
Average age at onset of ulcer symptoms	35 years
Ratio of males to females	5.5 : 1
Occupation: Manual labor	703
Clerical work	442
Housework	290
Location of ulcer: Duodenal	1,167
Gastric	215
Gastric and duodenal	53

* All the patients entering the wards or outpatient department of the Peter Bent Brigham Hospital from its opening in 1913 to Jan. 1, 1932, are included.

From the clinical observation it is difficult to believe that the acid factor is the only one which operates to produce the localized destruction of mucous membrane that is called peptic ulcer. Until further studies throw more light on the etiologic factors responsible for the syndrome one can do no more than obtain a clear understanding of the behavior of the disease.

Chronicity of Peptic Ulcer.—In 1929 we [1] stated: "All evidence points to the fact that ulcer is a chronic disease and that all the present methods of treatment are merely palliative. Cure probably is rare." The data pointing to the chronicity of the disease are now so complete that it is impossible to doubt their accuracy. This becomes evident

3. Lindau, A., and Wulff, H.: The Peptic Genesis of Gastric and Duodenal Ulcers, Surg., Gynec. & Obst. **53**:621 (Nov.) 1931.

4. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcers: I. Achlorhydria, Arch. Int. Med. **38**:603 (Nov.) 1926.

from (1) an analysis of the course of the disease, (2) the results of treatment and (3) roentgenologic and histologic studies.

Brown [5] stated that following the Sippy treatment 49.5 per cent of patients were cured and 16.7 per cent greatly improved. Stowell [6] noted that one half of the patients discharged from a London hospital suffered a relapse in succeeding years. Fremont-Smith and McIver [7] found that in only 66 per cent of their surgical cases did symptoms disappear entirely after several years. Walton [8] had immediate and satisfactory results in 67 per cent of his male and in 76 per cent of his female patients, but after some years only 20 per cent of the men and 40 per cent of the women had been relieved. In 1,350 cases in which operation for peptic ulcer was performed in his clinic, Wanke [9] found that 110 patients had to have a second operation for a recurrence of symptoms. Thirty-seven per cent of Forsyth's [10] patients suffered a relapse from one to seven times in from one to twelve years. Lahey [11] found that the results of surgical and of medical treatment were practically the same at the end of five years and that at that time treatment had been successful in only slightly more than 50 per cent of the cases. Alvarez [12] and Hurst [13] were impressed with the chronicity of the disease, and Brooks [14] said: "Until the cause of peptic ulcer has been definitely demonstrated we should not speak confidently of the cure of the condition but rather of mitigation of certain of its signs and symptoms. We [referring to physicians and surgeons] are neither of us curing the disease."

5. Brown, R. C.: Ulcer of the Stomach and Duodenum, in Christian, Henry A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1931, vol. 3, chap. 3, p. 172.

6. Stowell, in Kemp, R. C.: Diseases of the Stomach, Intestine and Pancreas, ed. 3, Philadelphia, W. B. Saunders Company, 1917, p. 295.

7. Fremont-Smith, M., and McIver, M. A.: Late Results of Surgical Treatment of Peptic Ulcer Based on a Study of Six Hundred and Seventy-Eight Cases, Am. J. M. Sc. **177**:33 (Jan.) 1929.

8. Walton, A. J.: The Results of Surgical Treatment of Gastric and Duodenal Ulcer, Brit. M. J. **2**:784 (Nov. 3) 1928.

9. Wanke, R.: Operierte chirurgische Misserfolge des Ulcusleidens und der chronischen Gastritis, Deutsche Ztschr. f. Chir. **220**:263 (Nov.) 1929.

10. Forsyth, D.: Duodenal Ulcer Among Medical Men: A Comparison of the Results of Surgical and Medical Treatment, Brit. M. J. **1**:780 (May 3) 1924.

11. Lahey, F. H.: The Management of Peptic Ulcer, New England J. Med. **205**:321 (Aug. 13) 1931.

12. Alvarez, W. C.: What Is the Risk of Insuring Applicants with Peptic Ulcer? Am. J. M. Sc. **178**:777 (Dec.) 1929.

13. Hurst, A. F.: Recent Advances in the Treatment of Gastric Diseases, Brit. M. J. **2**:779 (Nov. 3) 1928.

14. Brooks, H.: The Selection of Cases for Medical or Surgical Treatment in Gastric and Duodenal Ulcer, Boston M. & S. J. **198**:339 (April 5) 1928.

The untreated peptic ulcer pursues an up and down course for many years. The symptoms fluctuate, with spontaneous remissions and relapses. This has long been recognized as a cardinal point in the diagnosis of the disease. The interval between attacks may vary from weeks to months or years. Three patients in our series stated that for twenty years they had been without trouble of any sort. There are also many persons with peptic ulcer whose symptoms are so mild or so infrequent that they never seek medical aid. The ulcer is found incidentally either at necropsy or in the course of investigation for some other reason. Persistence is a quality which all attribute to ulcer before treatment. This is shown in the designation "chronic peptic ulcer." It is seen in the long duration of symptoms before patients apply for relief, which averages seven years in our series. It is implied in the old surgical aphorism, "Don't operate until after seven medical cures." It has taken a long time to show that it is just as true after all forms of treatment have been utilized.

Finally, roentgenologic studies furnish indisputable proof of the chronicity of ulcer, as we [15] have pointed out elsewhere. Crohn [16] and his co-workers have demonstrated the temporary nature of the disappearance of a crater in the stomach. They have treated gastric ulcers until the crater has disappeared as shown by the roentgenograms. Then, when the region was excised at operation the ulcer was found to be healed or in the last stage of healing. However, if operation was delayed until a return of symptoms occurred the ulcer was found to be present. Nicholas and Moncrieff [17] have shown the association between a gastric crater and the presence of symptoms. By observing patients with the roentgen rays for a long enough time they have been able to show that a spontaneous remission of symptoms is accompanied by a spontaneous disappearance of the crater and that the return of symptoms is associated with a reappearance of the niche. That duodenal ulcers behave in a similar way has been shown in the last three years by Dr. M. C. Sosman at the Peter Bent Brigham Hospital.

Because of all this it becomes evident that treatment must not be directed solely to curing the ulcer. Time alone may do that. It must seek to prevent the appearance of other ulcers, which is called relapse.

Factors Influencing Relapse.—If one cannot free the patient from the disease it should be helpful to discover how best to fit him to it.

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15. Emery, E. S., Jr., and Monroe, R. T.: Peptic Ulcer: The Diagnostic Value of the Roentgen Ray Before and After Treatment, Am. J. Roentgenol. **25**:51 (Jan.) 1931.

16. Crohn, B. B.; Weiskopf, S., and Aschner, P. W.: Life Cycle of Peptic Ulcer, Arch. Int. Med. **35**:405 (April) 1925; The Healing of Gastric Ulcers, ibid. **37**:217 (Feb.) 1926.

17. Nicholas, F. G., and Moncrieff, A.: Healing of Gastric Ulcers: Radiological Observations, Brit. M. J. **1**:999 (June 4) 1927.

To what are relapses due? We have been interested in this question for the last seven years. Often no cause is assignable; they seem quite spontaneous. But we have been impressed by the frequency with which three factors—fatigue, emotion and infection—seem responsible. Fatigue arising from too long hours of work, exhausting work or a poorly arranged schedule (night work) preceded a relapse in 334 of 1,279 patients that were studied in this regard. Emotional excitement, anger, worry, grief, too much social distraction and the like were the reasons for relapse in 258 cases. Infections, particularly of the upper respiratory tract, were found to precede a relapse in 167 cases. It is striking that only 37 patients believed that indiscretions in diet were the cause. Severe infections, such as pneumonia, rarely seemed to cause ulcer distress. Patients with ulcers require rest in bed and often attention to diet, in other words, some measure of medical treatment which is good for ulcer. It is rather the minor diseases—colds and grip—which do not enforce rest which bother the patient with an ulcer. Such conditions may be concerned in part with the variations in the spring and fall which we have noted and which Hutter [18] has emphasized; but the seasonal incidence of relapses is at times so striking as to cause speculation about some derangement of metabolism.

Frequency and Duration of Remissions.—Periods of freedom from ulcer distress are an integral feature of the disease, although the frequency and duration of relief vary within wide limits in different patients. Of the 500 patients questioned particularly on this point the remissions seemed definitely spontaneous in 131; vacation gave relief in 5, whereas in the others the remissions were associated with some form of treatment. Experience and the advice of friends and relatives frequently afforded the patients some degree of medical advice without resort to a physician.

While a large number of patients had remissions lasting only months or weeks or for so short a time as almost to escape their attention, it is obvious that the duration varies a great deal. Six patients had remissions lasting up to two years; 95, up to three years; 35, from three to six years; 2, from six to nine years, and 3, for twenty years.

Prognosis.—Ulcer is rarely a fatal disease. In our series of 1,435 patients, of 161 who died, only 87 (6.0 per cent) died from ulcer. Hemorrhage was the cause of death in 20, perforation in 28, obstruction in 4 and associated diseases and complications in 35. These cases have been analyzed fully and will be reported on in another article. Our impression is that death from ulcer should be still less common in the future. This is quite different from the experience of a generation ago,

18. Hutter, K.: Etiologic Relation Between Seasonal Variations and Occurrence of Ulcers, Arch. f. klin. Chir. **151**:651, 1928.

when the disease was regarded as a serious risk. Since that time, however, the situation has changed in several important respects. Then only the severe cases with some complication were recognized. The increasingly frequent use of the roentgenogram now results in earlier diagnosis and in the recognition of mild cases which were formerly classified as cases of hyperacidity. Medical and surgical treatments have been improved, and the indications for each have been more clearly defined.

Moreover, peptic ulcer does not tend to shorten the victim's life. The average age at death in our 87 patients who died of ulcer was 59. This is the life expectancy for the general population. Ulcer is important largely because of the economic risk it entails. It may cause a loss of time from work, alter schedules of living, narrow one's range of

TABLE 2.—*Incidence of Complications According to Duration of the Disease in 1,435 Cases of Peptic Ulcer*

Duration of Symptoms, Years	Number of Cases	Percentage with Complications
1	83	38.6
2	103	34.9
3	109	36.6
4	81	39.5
5	98	30.6
6–10	368	48.0
11–15	229	48.9
16–20	156	41.6
21–30	140	58.5
31–40	44	45.4
41–50	22	45.4
51	2	100.0

activity and compel attention to diet and food habits. These restrictions may prove to be blessings in disguise, for they force a person to live within his physical capacity from early middle age onward.

It is also reassuring that in general a peptic ulcer has little tendency to become worse as time goes on. Of 1,012 patients on whom data are available no change in the condition of the ulcer has developed in 872 (86.2 per cent). Obstruction has appeared or increased in 26; hemorrhage occurred in 49 who had not bled previously; pain has increased in 33; perforation resulted in 10; jejunal ulcers, in 20, and an hour-glass contracture, in 2. That the patients in whom the ulcer shows no change are not always those followed for the shortest time is shown in table 2, in which the duration of the ulcer has been determined by adding to the duration of symptoms before treatment the interval from the first to the last visit to the hospital. The surprisingly small change in the incidence of complications with advancing years is apparent. Up to the fifth year complications occurred in about 36 per cent of the cases; thereafter the incidence progressed to about 48 per cent.

We have been unable to find any means for predicting in which patients complications will develop and in which they will not. Some have a hemorrhage or perforation at the onset and live for years with little or no trouble. Others go on for years with only mild distress and then get into trouble. One man of 70 was seen with a duodenal ulcer and moderate symptoms that began at the age of 25; under medical treatment he had a good measure of relief until the age of 75, when prostatic hypertrophy caused urinary obstruction and he had a gross hemorrhage; treatment again helped, and he is still in good condition.

TABLE 3.—*Duration of Observation of 1,435 Patients with Peptic Ulcer*

Years	Number of Cases	Percentage
0	177	12.3
To 1 year	242	16.9
1–5	683	47.5
6–10	229	15.9
11–15	85	5.9
16–20	15	1.0
21–25	2	0.1
25+	2	0.1

TABLE 4.—*General Summary of the Results of Treatment of 1,435 Patients with Peptic Ulcer* *

	Final Results on All the Patients		Results of Surgical Treatments		Results of Medical Treatments		Results on Untreated Patients	
	No. of Patients	Per-centage	No. of Patients	Per-centage	No. of Patients	Per-centage	No. of Patients	Per-centage
No symptoms	221	17.5	91	19.0	149	13.7	30	23.8
Very few symptoms	411	32.6	93	19.3	397	36.5	11	8.7
Definite improvement	389	30.9	119	24.8	335	30.8	20	15.8
Improvement	65	5.1	39	8.1	69	6.3	5	3.9
No improvement	172	13.6	138	28.7	135	12.5	60	47.6
Totals	1,258		480		1,085		126	
No follow-up	177				48 / 126			

* The final status of the 1,258 patients that were followed is shown in the first column. In the other columns are grouped the results of the main classes of treatment.

RESULTS OF TREATMENT

A survey of what has been accomplished by treatment in this group of patients with ulcers should prove helpful in arriving at a decision as to the best way to manage the disease. The average duration of observation is three and nine-tenths years (table 3), but since 23 per cent of the patients have been followed for more than six years, a reasonably long range view is included.

When we estimate carefully the final results of treatment (table 4) we find that in the group which received treatment there are fewer patients without symptoms than among those whose ulcers were not treated; 17.5 per cent had no symptoms as compared to 23.8 per cent.

Yet this is exactly what is to be expected from the nature of the disease. The untreated patients form a control group which shows the natural history of ulcer and against which we must measure our efforts to alter its course. They were persons in whom the lesion was seen at necropsy or in life during the course of investigation for other conditions. That such a large proportion of them had never had trouble from their ulcers emphasizes our statement that no treatment has proved to be of curative value. On the other hand, about half of the untreated patients were unimproved, and only in one fourth did care given to other complaints appear to improve the ulcer.

Thirty-two per cent of the patients who received treatment had very few symptoms thereafter. They might reasonably be classified as cured, had not careful personal interviews demonstrated that on occasions they still experienced a mild distress similar to that which they had before

TABLE 5.—*Reasons for Failure in 1,085 Cases of Medical Treatment and 480 Cases of Surgical Treatment*

	Medical Treatment		Surgical Treatment		No Treatment	
	No. of Patients	Per-centage	No. of Patients	Per-centage	No. of Patients	Per-centage
Pain	386	35.5	197	41.0	52	41.4
Hemorrhage	88	8.1	73	15.2	19	15.0
Obstruction	52	4.8	42	8.7	12	9.5
Hypersecretion	73	6.7	42	8.7	5	3.9
Perforation	12	1.1	8	1.7	24	19.1
Hour-glass contracture	7	0.6	7	1.4	4	3.1
Jejunal ulcer	0		47	9.7	0	

coming to the hospital. An almost equal number were unquestionably better; 5.1 per cent were improved in a minor degree, and only 13.6 per cent showed that the treatment had definitely failed. Thus 81 per cent of the patients were successfully treated—a figure which is in substantial agreement with the published results obtained in other clinics.

In analyzing the results of specific therapeutic measures it was necessary to distinguish between treatments and patients. Many patients had more than one operation, or several distinct medical schedules, and the value of each was estimated at the beginning of the next. A comparison of the medical treatments with the surgical (table 4) shows that operations gave a higher percentage of continuous relief, which should be predicted from the permanent character of some of them. But the surgical failures were more than double the medical failures, and the proportion of satisfactory results was distinctly lower.

The reasons for failure of treatment are shown in table 5. The parallelism of the medical and surgical groups is obvious. It is worthy of emphasis that in general surgical intervention was less fortunate than medical treatment in warding off pain, hemorrhage, obstruction, perforation and hour-glass contractures. Jejunal ulcers followed 11.3

per cent of gastro-enterostomies, 12 per cent of gastro-enterostomies with resection of the pylorus or a portion of the stomach, 23.1 per cent of those with excision of the ulcer and 16 per cent of those with transection of the pylorus. Seven jejunal ulcers perforated into the colon, causing gastrocolic fistulas.

This apparently unfavorable result of surgical treatment may be explained in one of two ways. Patients who were operated on had ulcers more difficult to treat or more severe. Perforation and obstruction are not treated medically. Eighty-one per cent of the surgical cases and only 60 per cent of the medical cases showed a definite complication of the ulcer. The results in such cases may be expected to be worse than in simpler cases, particularly when second and third operations are performed. That this is not the whole explanation, however, is shown by a study of table 6, which shows that in uncomplicated

TABLE 6.—*Results of 426 Medical and 90 Surgical Treatments in Patients with Peptic Ulcer Without Complications* *

Results	Medical Cases		Surgical Cases	
	Number of Cases	Percentage	Number of Cases	Percentage
No symptoms	86	20.1	24	26.4
Very few symptoms	184	43.1	18	20.0
Definitely improved	112	26.3	22	24.4
Improved	15	3.5	10	11.1
Unimproved	29	6.8	16	17.7

* A comparison with table 2 shows that the ratios are the same as for all the cases.

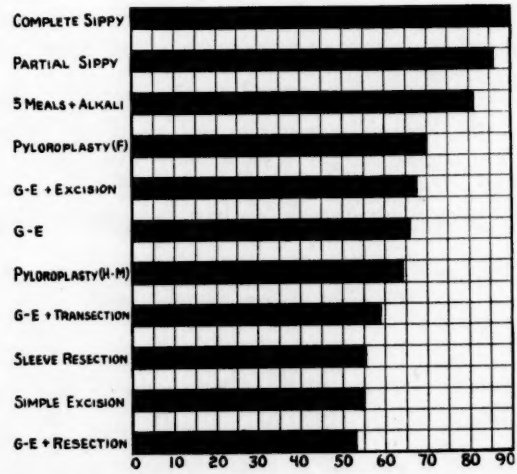
cases the proportions of good and poor results are essentially the same as for the whole group (table 4).

Surgical intervention appears to be just as unable to alter the course of peptic ulcer as medical treatment, and the true explanation for the unsatisfactory results seems to be that patients who have been operated on have not been offered or have not accepted so much attention to their general health and after-care as those treated medically. Physicians have had the feeling that surgical intervention may cure while medical measures would only relieve, and they have been inclined to tell patients after their operation to forget that they ever had an ulcer. While the physicians have been completely disillusioned on this score, the patients have not been. It is still difficult to persuade them of the necessity of after-care in the way of diet and attention to general hygiene, rest, care of infections and other measures designed to prevent relapses.

The same point is demonstrated in a survey of the results of individual types of treatment (table 7 and chart). All the medical measures gave better results than the surgical. An important reason for this is that these patients received much more attention. They had been taught the nature of their disease and were willing to report when asked and

to take good care of themselves. Patients who were operated on were harder to impress as to the necessity of after-care, being prone to consider themselves cured and immune from relapses.

The patients who took a complete Sippy [19] treatment are known to have had complete neutralization of their gastric contents for from nine



Percentage of satisfactory results obtained in 480 surgical and 1,085 medical treatments of peptic ulcer.

TABLE 7.—*Results of 1,565 Therapeutic Measures in 1,258 Patients with Peptic Ulcer*

Type of Treatment	Number of Cases	Percentage with No Symptoms	Percentage with Very Few Symptoms	Percentage Definitely Improved	Percentage Improved	Percentage Unimproved
Five meals, alkaline powders	938	13.1	36.7	30.3	6.4	13.3
Partial Sippy treatment	89	13.4	38.2	33.5	6.7	7.8
Complete Sippy treatment	58	25.0	31.0	34.4	5.1	5.1
Gastro-enterostomy	238	22.6	18.9	24.7	6.2	27.3
Gastro-enterostomy with excision of ulcer	34	23.5	20.6	23.5	11.8	20.6
Gastro-enterostomy with resection of stomach	58	13.8	24.1	15.5	5.1	41.3
Gastro-enterostomy with division of pylorus	31	16.1	12.9	29.3	3.2	38.7
Pyloroplasty (Finney)	43	20.9	25.3	25.5	11.7	18.6
Pyloroplasty (Heineke-Mikulicz)	11	9.0	18.1	36.3	9.0	27.2
Simple excision	56	8.9	17.8	28.5	16.2	28.5
Sleeve resection	9	11.1	11.1	33.3	11.1	33.3

to twelve months. Those who followed the treatment for from four to nine months or who failed to maintain neutralization were said to have had a partial Sippy treatment.[11] All the others are grouped under the

19. Sippy, B. W.: Gastric and Duodenal Ulcers: Medical Cure by an Efficient Removal of Gastric Juice Corrosion, J. A. M. A. **64**:1625 (May 15) 1915.

heading "five meals and alkaline powders"; they received a bland, non-irritating diet with one or more interpolated meals. They also received variable amounts of alkaline powders, although no attempt was made to neutralize the gastric acidity completely. This group also included patients who were started on the Sippy treatment while in the hospital but failed to keep it up after being discharged, often owing to the fact that it conflicted with their work. That the best results were obtained with the complete Sippy regimen may be due, as some believe, to a more complete healing of the ulcer, but it is our impression that the maintenance of a rigid schedule is the more important factor. This is suggested also by noting that the next best results followed a partial Sippy treatment and that the poorest results followed the rather lax "five meal and alkaline powder" program. The outcome seemed to vary according to the willingness of the patient to follow directions in detail as to his habits of living. Many of the patients in the "five meal" group really achieved more neutralization than some of those who took a partial Sippy treatment but were led to believe in a false security because of freedom from symptoms and paid less attention to general hygiene and rest.

None of the operative procedures attained as high a degree of satisfactory results. A simple posterior gastro-enterostomy, sometimes with plication of the pylorus, was the commonest operation, and it proved almost as effective as when excision of the ulcer was added to it. Pyloroplasty in some form was in the same rank. Distinctly less favorable results followed operations in which the surgeon thought it necessary to add a division (transection) of the pylorus or removal of the pylorus or some portion of the stomach. In these cases the patients also proved most refractory to subsequent medical treatment. Removal of the antrum was proposed with the idea that the loss of its hormone would decrease the production of hydrochloric acid. Experience has shown this to be a mistake. Since the operation removes the part of the stomach which has an alkaline secretion it should be abandoned.

Other types of operation gave equally poor results, but they were often performed on patients who were in bad condition, had adhesions or had suffered acute perforation, so that no other course was open. The figures are not a criticism of the procedure but simply an illustration of the difficulties of the situation. We are getting better surgical results since the choice of operative procedure has been guided by a knowledge of the possible results and since the postoperative care is applied early and is kept up. We have long since rid ourselves of the notion that one form of therapy is far superior to all others. We recognize that success depends on an acquaintance with all forms and on the ability to use whichever fits the individual case.

Table 8 shows that the longer one follows patients with peptic ulcer, the fewer are his medical "cures." Surgical "cures" maintain themselves at a consistently higher level after the first year. Medical failures also tend to become fewer as time goes on, and so do those following surgical procedures. In other words, more and more cases fall into or are lifted up to the ranks of the satisfactorily improved.

TREATMENT OF ULCER AS A CHRONIC DISEASE

Treatment of Uncomplicated Peptic Ulcer.—Two convictions were brought home to us early in our experience with cases of peptic ulcer. One was that the disease is primarily a problem for the physician, and the other, that the strict Sippy regimen was the best medical solution. Time has clarified these views. Surgical intervention is at times indispensable, even life-saving, but it does not cure the disease or alter its

TABLE 8.—*Influence of the Duration of Observation on the Number of Cures and Failures in the Treatment of Peptic Ulcer*

Period of Observation in Years	Number of Patients Cured		Number of Patients Unimproved	
	Percentage with Medical Treatment	Percentage with Surgical Treatment	Percentage with Medical Treatment	Percentage with Surgical Treatment
0- 1	21.4	7.9	17.4	39.4
1- 2	16.3	23.3	6.0	28.3
2- 3	15.3	38.8	9.2	24.0
3- 4	16.6	15.6	9.5	19.5
4- 5	13.8	14.8	2.7	25.9
5- 6	7.4	19.0	9.2	19.0
6-10	8.4	22.9	4.6	5.4
11-15	7.4	18.5	14.0	11.1

tendency to persist. Since it carries a mortality which equals or exceeds the chance of the patient with ulcer to die of the disease at the age of 59, it should be used sparingly and only for very definite indications. How, then, shall one go about the treatment in a case of duodenal ulcer and no complication—the average case?

In the first place, the importance of a thorough study of the case is to be emphasized. A complete physical examination is required, as well as routine analyses of the blood, urine and stool, a Wassermann test and a gastric analysis. One must acquaint himself with the past history of the patient, with the details of the status of the systems other than the gastro-intestinal tract and with the social and economic situation. Obviously, certain diseases, such as cholecystitis and intestinal disturbances, may have an important influence on the symptomatology of the peptic ulcer and may compel alterations in its treatment. Other diseases, such as carious teeth and recurrent infections of the tonsils, may affect the ulcer by disturbing the general state of health. It is impossible to

treat the ulcer alone. When a physician accepts the responsibility for such a case he must be prepared to treat, or superintend the treatment of, the whole person. He must be alert to the need for repeated physical and laboratory examinations, lest he overlook complications or intercurrent disease—errors lying in the path of all who deal with chronic disease.

We have found it wise to tell the patient frankly the nature of his disease. We tell him that the ulcer does not seriously threaten his life and does not tend to progress in severity, although it may interfere with his comfort and his activity from time to time. We confess that there is no known means of effecting a permanent cure but reassure him that there are various conservative measures which are able to make him comfortable and efficient at work, and we advise him as to the necessity of henceforth reporting regularly to his doctor. We have pursued this policy for the last six years, both with patients at the clinic and with private patients, and we have been greatly impressed with its value. It generates a spirit of cordial and intelligent cooperation. Most patients are secretly convinced of the chronicity of their trouble before the physician sees them. When their fears are confirmed and allayed they are transformed from a restless, dissatisfied group wandering from doctor to doctor into one that realizes the need for daily care, for attention to hygiene and for occasional medical investigation.

It is necessary to discover any causes that may account for the activity of the disease in each particular patient. If he is of a worrisome disposition or unstable emotionally he must be shown the importance of leading an even-tempered existence for the sake of his ulcer. One man, a dentist, not included in this series, has found that he pays for an outburst of anger by a few days of ulcer pain, and he has achieved a comfortable existence by becoming phlegmatic. Even if the patient is a perfectly calm person he will learn the wisdom of resorting to treatment for his ulcer during mental or economic crises. We are impressed by the number of patients with intractable pain and by the number of those that require prolonged, meticulous attention to treatment who by nature or by force of circumstances are exposed to much nervous wear and tear. Others are not bothered by such factors but have trouble during periods of physical fatigue. Still others find that minor infections of the respiratory tract are their only consistent enemy. It is the task of the physician to study these individual characteristics and to include their elimination in his treatment.

Rest is absolutely essential in the treatment of every patient with ulcer, but the problem of how much rest is needed cannot be settled in general terms for all the cases. Sippy advised hospitalization for a month; others still insist on this or its equivalent in any other neutral environment. Although this is essential in some of the more severe

cases it is not necessary for many patients, to some of whom it is a great economic hardship. Some patients do well with a few more hours in bed each day than they have been accustomed to allot themselves. At first they may require twelve hours each night, and a midday nap; later they may find nine hours sufficient. It is our experience that less than eight hours of rest each day is suboptimal and may result in the accumulation of enough fatigue to precipitate an attack of ulcer pain or to prevent healing in the active stage. Mild hypnotics may be useful for short periods to counteract insomnia due to nervous fatigue. The individual patient must determine, with the supervision of his physician, how much and what sort of rest and relaxation he requires, not only during the stage of symptoms but for the free intervals as well. The variety of patients' occupation and pursuits at times calls for the exercise of much ingenuity.

The diet must meet several requirements. 1. It must have balance; there must be no lack of necessary minerals, vitamins and food substances. Too rigid restrictions are unwise when the treatment must be so prolonged, and there are reports in the medical literature of deficiency diseases occurring as a result of such restrictions. 2. It should consist of foods which are not too coarse. This means that meats must be chopped finely and vegetables must be strained. Ivy [20] has shown that a diet of bland foods allows an artificial ulcer to heal more rapidly than a diet of coarse foods. A few patients can be trusted to masticate food so thoroughly that the preparation of their food need not be different from that of other members of their family. For most patients it is wiser to insist that their food must permanently receive these attentions. 3. Finally, condiments should be used sparingly, although a minimum necessary for palatability may be allowed. Alcohol in any form and carbonated drinks seem definitely contraindicated. We are rather lenient as to tobacco. Some of our patients smoke without any apparent harm, and they need not be denied this solace in moderation. Others find by trial that irritation of the ulcer is caused by smoking, and they should become abstainers.

Alkalis are useful for the relief of pain in the early stages but do not aid healing unless complete neutralization is accomplished. However, their use should be discouraged so far as possible in order to prevent the patient's relying on them to the neglect of other measures which do promote healing. They can be satisfactorily given according to Sippy's formula (calcium carbonate, 0.6 Gm., sodium bicarbonate, 2 Gm.). They may be given in individual powders, in bulk or in tablet form. When

20. Ivy, A. C., and Fauley, G. B.: Factors Concerned in Determining Chronicity of Ulcers in Stomach and Upper Intestine: II. Effect of Diet on Healing of Acute Gastric Ulcer, Am. J. Surg. **11**:531 (March) 1931.

constipation requires attention magnesium oxide as suggested by Sippy is useful. These powders have proved to be so satisfactory that we have not found it necessary to use other alkalis, such as precipitated calcium phosphate.

Belladonna in some form is occasionally valuable for patients who have intestinal distress. It does not seem to affect the ulcer distress. Our experience with mucin has not been satisfactory, and we have discarded it because it is unpleasant to take.

The diet and the schedule advocated by Sippy meet all the requirements. By the use of this treatment it is possible to control completely the corrosive action of the gastric juice, which no modification can do. The difficulty of its application would be no argument against it if it could effect permanent cures. Our experience has been, however, that patients tend to relapse as frequently after the Sippy treatment as after any other if they are permitted to return to their former mode of living. Moreover, as Nicholas and Moncrieff [17] have pointed out, ulcers heal in the presence of hydrochloric acid, so that complete prolonged neutralization is not necessary. In most of our uncomplicated cases, therefore, we have abandoned the Sippy regimen, particularly for patients who find it an economic hardship, cannot leave their work or cannot continue it after returning to work.

A "modified Sippy regimen" is of course no different from any other plan which relies on frequent feedings and doses of alkaline powders. Symptoms of ulcer disappear quickly following any of them, but if the general situation is not controlled an active, open ulcer may persist and make itself known just as quickly when the treatment is stopped. The powders may be used for only a few weeks or months; dietary restrictions may be eased later on, but rest from physical and nervous fatigue, avoidance of infection and care of other factors must be insisted on if the treatment is to be made really adequate.

What is to be done if this treatment fails to "cure"? Such a lack of perfection is to be expected from the nature of the disease, but this does not mean that very good results are not possible. A patient with peptic ulcer has an active or potentially active lesion for the rest of his life, so far as we can tell. Treatment does not stop with the clearance of symptoms or a short time after, as it used to. The general hygienic measures are continuous; the use of alkaline powders and strict diet schedules may be repeated as often as necessary and are always effective in uncomplicated cases. One should not lose faith in the treatment because of relapses, and resort impatiently to more radical measures. In some cases complications will develop—there is no sure way of telling in which ones this will occur. The complications will be treated sooner if the possibility of their occurring is always borne in mind than if a remission is regarded as a cure. It is our conviction that the number

of complications has decreased since we have established permanent supervision.

Uncomplicated gastric ulcers are to be treated in the same way, although they require closer supervision. It has been our experience [1] that such ulcers are or become malignant in only about 5 per cent of the cases. Because the experience at the Mayo Clinic [21] has been quite different, because there is no way of telling offhand whether any particular case is benign and because of Holmes' [22] recent emphasis on the dangers of lesions about the antrum we established the following plan, which has worked satisfactorily: A patient whose roentgenograms show a gastric ulcer is required to stay in the hospital for three weeks on a strict Sippy schedule, and the roentgenographic study of the stomach is repeated. If this shows no healing as compared to the first examination immediate operation is advised. If the healing is definite, the ulcer crater being smaller, medical treatment is continued. Roentgen studies are made again three months and six months later and then at least once a year, to make sure that this confidence is justified.

Treatment of Peptic Ulcer Causing Obstruction.—It is important to distinguish between retention and obstruction. With the present reliance on the roentgenologist for diagnosis there has been a strong tendency for the physician to assume that the two terms are synonymous. Fluoroscopic evidence that radiopaque material has remained in the stomach for six hours does not tell why it has done so. Obstruction is the retention of material in the stomach for an abnormal period of time owing to cicatricial narrowing about the ulcer. However, retention may be due to other causes, such as apprehension over the examination, headache or nausea, local swelling and edema about an ulcer or pylorospasm. A distinction between these temporary and permanent factors can be made by the repetition of the roentgen study after a short test of medical treatment and by a comparison with the clinical findings, such as a history of vomiting of food for some time with a loss of weight and the demonstration of food residues in the fasting stomach.

These facts, which are well known to roentgenologists and students of the disease, were pointed out by us in an earlier paper.[15] It was also suggested there that barium sulphate is an abnormal material for the stomach to deal with and that what the physician who treats the patient needs to know is how ordinary food fares in the stomach. In some cases the heavy salt pours through the pylorus so rapidly as to cause a

21. Alvarez, W. C.: Diseases of the Stomach, in Christian, Henry A.: Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1931.

22. Holmes, G. W., and Hampton, A. O.: Importance of Location in Differential Diagnosis of Benign and Malignant Gastric Ulcerations, New England J. Med. **208**:971 (May 11) 1933.

real obstruction to be missed; in a few other cases it settles in the region of the stomach below the obstruction, and overemphasizes the true state of affairs. Therefore, surgical measures need not be advised indiscriminately for all cases of retention.

Statistics on our present series of cases show that obstruction of some degree was found in 169 cases (11.7 per cent). Of 266 cases in which a comparison of the roentgen and clinical evidence of retention could be made, there was agreement in 141 (53 per cent). This was most common in the cases in which a large residue was shown by fluoroscopic examination (71 per cent of the cases showing from 30 to 60 per cent retention, and 91 per cent of those showing from 60 to 100 per cent retention at six hours). Disagreement between the results obtained by the two methods occurred almost entirely in the cases in which small residues were observed under fluoroscopic examination (29 per cent). The 9 per cent showing a large roentgen retention but no clinical obstruction were the cases of reflex spasm due to headache, nervousness, etc.

Medical treatment was much less satisfactory in the cases showing clinical confirmation of the roentgen evidence of obstruction than in the others. Medical treatment was effective in only 38.6 per cent of the cases in which the gastric aspirations and the history agreed with the roentgen findings. It helped in 68.2 per cent of the cases in which the roentgenogram alone suggested retention. Surgical treatment was much more efficacious in patients with high grade obstruction than in those with less than 40 per cent retention. Below this level medical and surgical measures were equally effective.

It seems wise, therefore, in every case to test the roentgen evidence of obstruction with the clinical evidence and with a short trial of careful medical treatment. If the two disagree and the six hour retention is small such a treatment is apt to be sufficient, for it is unlikely that an important degree of permanent blockage is present. If the two agree and the large residue persists on a second roentgen examination it is useless to delay operation any longer.

Treatment of Peptic Ulcer with Hemorrhage.—Hemorrhage is a dramatic complication of peptic ulcer, terrifying to the patient and his friends and by its threat of a calamitous outcome often impelling the physician to use extravagant therapy. A knowledge of what the average hemorrhage means to the average patient with ulcers proves of great comfort to all the parties concerned, and suggests a reasonable plan of treatment.

In our previously reported series [1] the incidence of hemorrhage was 34.8 per cent, a figure which was in agreement with most early statistics. Now, with the number of cases nearly trebled, we find only 384 patients, or 26.7 per cent, who have bled at some time. This decrease is probably

due to the recognition of many milder cases rather than to any improvement in our method of treatment, for other recent writers have noted an even lesser incidence. It is perhaps fair to state that 1 of every 4 patients with ulcer will suffer from a hemorrhage at some time in his life.

There is no way of telling which patients will bleed. Some do so at the apparent onset of the disease, others at later periods even up to fifty years after the onset. Some seem to have a persistent hemorrhagic tendency, and others "outgrow" it or acquire it. Up to 1932, 20 of our patients, that is 5.2 per cent of those who have bled or 1.3 per cent of the total number, died of hemorrhage. Thus a hemorrhage from a peptic ulcer carries only a small threat to life. Its economic importance is greater, for it forces the patient to leave his work and incur expenses of hospital and professional attendance for weeks.

Hemorrhage presents two problems in therapy: how to deal with the acute stage and how to prevent a future loss of blood. Surgeons naturally prefer not to operate on an already anemic patient who is actively bleeding. But whenever one is called on to treat a patient who continues to bleed despite medical management there is a great urge to call for the help of surgical measures. As the incidence of death is less than the mortality associated with gastric operations it seems better to follow the rule that hemorrhage from ulcer is a medical problem entirely. In 95 per cent of the cases the bleeding stops spontaneously, and it is the job of the physician to prevent its recurrence. At present there is no way of saving the 5 per cent who continue to bleed until death supervenes, for it is only in this relatively small group that surgical intervention is justified, and unfortunately there is no way of telling which patients are going to fall in this group.

The belief is prevalent that patients are less likely to bleed after surgical than after medical treatment, and there is a tendency to advocate surgical intervention whenever a patient has had some severe bleeding. Our figures do not lend any justification to this belief. The relation of treatment to the incidence of hemorrhage has been recorded for 380 patients (table 9). Of 202 patients, 19.3 per cent have bled after medical treatment during an average period of observation of three and six-tenths years. Of 155 patients who received surgical treatment, 17.4 per cent had another hemorrhage within an average period of four and eight-tenths years. Even if we make a correction for the difference in the time of observation and allow for a greater tendency to bleed in the surgical cases it is still clear that surgical intervention does not prevent future hemorrhages any more than does medical treatment. Table 9 illustrates this fact in detail.

A single hemorrhage is therefore not an indication for surgical intervention. In spite of this fact clinical experience shows that a certain

number of patients who bleed frequently on medical treatment cease to bleed after operation. Therefore, when it becomes established that patients have a hemorrhagic tendency recourse should be had to surgical procedures. For the immediate treatment of the bleeding patient, we have had the best results with the plan established by Sippy.

TABLE 9.—*Occurrence of Hemorrhage in Relation to the Treatment* *

Type of Treatment	Number of Patients Treated	Percentage with Hemorrhage Before Treatment Only	Percentage with Hemorrhage After Treatment Only	Percentage with Hemorrhage Both Before and After Treatment
Medical	202	64.5	15.8	19.3
Surgical	155	61.9	20.6	17.4
No treatment	23	48.0	26.0	26.0

* The groups are similar, but there is a greater tendency for hemorrhage to occur after surgical than after medical treatment.

TABLE 10.—*Frequency with Which Complications Occurred in Relation to Various Amounts of Free Hydrochloric Acid in the Gastric Contents of 994 Patients with Peptic Ulcer* *

Free Hydrochloric Acid	Number of Patients	Percentage with No Complications	Percentage with Obstruction	Percentage with Hemorrhage	Percentage with Perforation	Percentage with Hour-Glass Contracture	Percentage with Jejunal Ulcer
0-20	128	53.9	13.2	22.6	3.9	1.5	4.6
21-40	224	46.9	22.3	22.3	3.1	2.2	3.1
41-60	290	47.2	20.6	22.4	3.1	2.7	3.7
61-80	214	47.6	18.7	25.7	3.2	0.4	4.2
81 plus	138	46.3	19.5	24.6	5.0	...	4.3

* No analyses were done on other patients. The highest level of free acid was taken in each case. The complications are strikingly similar at each level.

TABLE 11.—*Percentage of Satisfactory Results of Treatment in Relation to Different Grades of Acidity* *

Free Hydrochloric Acid	Number of Patients Showing Satisfactory Results	Percentage
0-20	73	63.4
21-40	135	66.1
41-60	191	72.6
61-80	130	68.7
81 plus	67	57.2

* The figures represent the highest amount of free hydrochloric acid in the 888 patients that were followed.

Treatment of Peptic Ulcer with Hyperacidity.—A small group of patients with ulcers respond poorly to all routine treatment. They are not long without pain on medical measures; pain at night is very common. They are usually of a very nervous temperament, and their gastric contents have high degrees of free acidity. Attempts to overcome this condition by increasing the administration of the alkaline powders results

in a still greater secretion of acid and in the appearance of toxic symptoms (alkalosis). In most instances surgical measures are followed quickly by the formation of jejunal ulcers, which are still more intractable. We therefore came to regard hyperacidity as a definite complication of peptic ulcer.

An analysis of our cases shows that this belief was wrong and that hyperacidity alone is not a complication. Table 10 shows the values for acid in the gastric contents of the 994 patients on whom analyses were made. Since the incidence of complications is the same whatever the level of free acid and since the acidity seems not to influence the results of treatment (table 11), whether medical or surgical, the severity of the ulcer cannot be judged by the height of the curve for acid. The difficulty lies rather in the amount of acid secreted. The stomach forms acid at a fixed concentration, and the figures from titration depend on the amount of neutralization which has taken place. High degrees of acidity may result from inadequate neutralization or from the production of greater quantities of acid than the normal processes can cope with. It is in patients with hypersecretion that difficulties of treatment are encountered.

The presence of hypersecretion may be suspected by the presence of the following conditions [23]: (1) the persistence of pain at night after the patient should be relieved by treatment; (2) an inability to neutralize the gastric acidity completely by means of the Sippy regimen, and (3) a tendency for the stomach to produce a greater quantity of acid as the amount of alkali is increased. Proof is forthcoming if a secretion persists in a fasting stomach. This is best determined, as suggested by Henning and Norpath,[24] by allowing a nasal tube to remain in the stomach during the night and performing frequent aspirations.

The presence of hypersecretion requires extreme caution in treatment. The patient must be confined to bed in a hospital for several weeks and be given frequent feedings of a very bland diet and milk and cream every hour. Alkaline powders are contraindicated. Sedatives are usually necessary to control nervousness and to secure restful sleep. After the symptoms are fully allayed the diet is gradually increased and the number of doses of milk and cream decreased until the schedule is that used in the uncomplicated case. Subsequent care and attention to general hygienic measures are also important. Since jejunal ulcers are prone to develop in these patients surgical procedures must be

23. Emery, E. S., Jr.: The Treatment of Peptic Ulcer Complicated by Hypersecretion, New England J. Med. **210**:637 (March 22) 1934.

24. Henning, H., and Norpath, L.: Investigations on Secretory Function of Stomach During Night Sleep, Arch. f. Verdauungskr. **53**:64 (Jan.) 1933.

avoided. Roentgen therapy is sometimes useful as a palliative measure in these cases in order to bring the condition under control.[25]

Treatment of Ulcer with Perforation.—It is generally recognized that acute perforation must be repaired surgically as soon as possible and that disasters increase rapidly as treatment is delayed. Difficulty in diagnosis was the usual cause of delay in our experience, many of our patients having entered the hospital from twelve to forty-eight hours after the onset. Ten patients had a chronic perforation which was recognized for the first time at the operating table or at necropsy. It seems that the only way to improve this situation is to consider every peptic ulcer as a potentially perforating ulcer for the remainder of the patient's life. While the incidence is small (111 cases, or 7.7 per cent), we know of no way of predicting in which cases perforation will occur. Certainly it has been demonstrated amply that roentgenologic reports of "perforating types" of ulcers are misleading, since they are no more likely to rupture than any other type. If the possibility is kept in mind, an acute abdominal upset in a patient with an ulcer may be distinguished as perforation at the earliest possible moment.

Simple closure of the perforation with or without gastro-enterostomy has proved effective, and the patients prove no more difficult to treat later than other patients with ulcers. In our series 18 (16.2 per cent) had no symptoms afterward, and satisfactory results were obtained in 66 (59.4 per cent). Thirty-five patients (31.5 per cent) were unimproved; 32 of these died, most of them being moribund before treatment could be instituted. Those who were in good condition were not harder to take care of than other patients who have been operated on. Seven jejunal ulcers perforated into the colon, causing a gastrocolic fistula and a very difficult technical situation for the surgeon.

SUMMARY

This study of a large group of patients with chronic peptic ulcer of the stomach or duodenum over a long period of years shows that the disease tends to persist throughout life when once it is established. It is caused by some factor or factors which are not yet known. More appears to be involved than the local lesion in the mucous membrane, which heals spontaneously or under treatment and then breaks down again. The disease is rarely fatal and does not generally shorten life. Although it is subject to certain complications, in the average case it does not tend to get worse as time goes on.

It is demonstrated that none of the present methods of treatment do more than assist in the induction of remissions, no matter how strict

25. Emery, E. S., Jr.: Peptic Ulcer: Its Treatment by Roentgen-Ray, New England J. Med. **206**:717 (April 7) 1932.

the medical schedule or how radical the operation. Surgical procedures produce longer periods of freedom from symptoms than medical treatment, but the former also carry a definite threat to life and often produce mechanical situations which make subsequent attacks difficult to control. A plan of conservative treatment is offered which seeks to produce the best possible results with the least cost to the patient. Its most important aspect is that it seeks to govern the patient's total situation, trying to prevent or minimize factors which may cause a relapse. The most important offenders known are fatigue, worry and infection. Surgical intervention is resorted to for definite purposes, namely, to close a perforation, to overcome a permanent obstruction of more than 40 per cent as seen by fluoroscopic examination six hours after a meal of barium and to attempt to overcome a hemorrhagic tendency; it is also resorted to in cases in which there is a reasonable suspicion of cancer or malignant degeneration. The operation of choice is that which accomplishes the specific purpose in view and interferes as little as possible with the physiologic action of the stomach. Subsequently the patient is to be treated as all other patients with ulcer who have not been operated on. During periods of hypersecretion the patient is to be treated with particular care medically; operation at such a time is disastrous.

TRANSVERSE DIAMETER OF THE HEART IN PATIENTS WITH HYPERTENSION

WITH CLINICAL MEASUREMENTS CHECKED BY POSTMORTEM STUDIES

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Since the advent of the use of roentgen rays in the diagnosis of cardiac disturbance, accurate measurement of the size of the heart has become a routine procedure. In the attempt to distinguish between the normal and the abnormal cardiac silhouette various measurements have been suggested,[1] of which the transverse diameter, because of the ease and accuracy of determination, has received the widest favor. However, it was found that average or arbitrarily set limits of the normal width were not reliable as a guide to cardiac enlargement in the individual instance. In 1919, Danzer [2] proposed the ratio of the transverse diameter of the heart to the internal diameter of the chest, determined on a roentgen-ray shadow on a film taken 6 feet (1.8 meters) from the tube, as a criterion of the normal size of the heart. He believed that there is a constancy of relationship between the two measurements, such that the ratio of 1:2 is not exceeded in normal persons despite variations in the body habitus. The data on which this assumption was based were not given. He admitted, however, that in thin-chested, asthenic persons cardiac hypertrophy and/or dilatation might be present, but were not evident by this method of measurement.

In 1926, Hodges and Eyster [3] attempted to define by statistical methods the normal transverse cardiac diameter as correlated with age, sex, height and weight. The width of the heart was determined on 80 persons by means of the orthodiagram, which obviates the exaggeration of the cardiac shadow and width of the chest inherent in the method of teleoroentgenography. Statistical analysis showed that nor-

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1. Eyster, J. A. E.: Determination of Cardiac Hypertrophy by Roentgen-Ray Methods, Arch. Int. Med. **41**:667 (May) 1928.

2. Danzer, S. D.: The Cardiothoracic Ratio: An Index of Cardiac Enlargement, Am. J. M. Sc. **157**:513 (April) 1919.

3. Hodges, F. J., and Eyster, J. A. E.: Estimation of Transverse Cardiac Diameter in Man, Arch. Int. Med. **37**:707 (May) 1926.

mally a correlation exists between the factors mentioned and the transverse cardiac diameter, most evident in the case of body weight. A formula was devised for predicting the normal width of the heart as disclosed by the orthodiagram in the individual instance. It was of such statistical accuracy that if the actual measurement exceeded the one predicted by as little as 5 mm. the chances were three to one that the enlargement was abnormal. However, they stated that this formula was only 19 per cent more accurate than an assumed average normal for all cases and little better than random guessing.

In a further study,[1] dealing with attempts to determine a closer degree of correlation between the size of the heart and bodily measurements, Eyster compared this standard with the Danzer ratio in 100 normal persons and in a similar number of persons with various types of heart disease. He found that by the cardiothoracic ratio 94 per cent of the group of normal persons had a transverse cardiac diameter less than one half the internal diameter of the chest, but that this was also true in 38 per cent of those with a pathologic condition. Only 42 per cent of the latter series had a ratio definitely indicative of cardiac enlargement. The prediction figures gave distinctly better results. Only 8 of 100 normal persons had actual transverse diameters above 10 per cent of the predicted normal, whereas 78 per cent of those with a pathologic condition had actual transverse diameters exceeding this figure. Bainton,[4] comparing these standards in 97 males and 75 females who had no evidence of heart disease, obtained a similar discrepancy, which will be dealt with in detail later. In a recent study,[5] the same observer applied the prediction figures of Hodges and Eyster to 470 patients, of whom 44 had functional cardiac disturbance, 70, a questionable diagnosis of cardiac involvement, and 357, organic heart disease. Seventy per cent of the latter had transverse cardiac diameters exceeding by more than 0.5 cm. the predicted normal. One hundred and thirty of the 357 in the pathologic series had hypertension, of whom 90 (69.2 per cent) had a similar degree of cardiac enlargement. He did not utilize the Danzer ratio in this study but, on the basis of his experience with "noncardiac" subjects, concluded that it is of little value in detecting cardiac enlargement, whereas he regarded the prediction figures of Hodges and Eyster as the most efficient standard in predicting the transverse diameter of the normal heart.

To our knowledge, the efficacy of these two standards in determining cardiac enlargement has been studied in only one series of pathologic cases. It was considered worth while to recheck the results in a series

4. Bainton, J. H.: The Transverse Diameter of the Heart, Am. Heart J. **7**: 331 (Feb.) 1932.

5. Bainton, J. H.: The Silhouette of the Heart and the Aortic Arch: Orthodiagraphic Measurements, Am. Heart J. **8**:616 (June) 1933.

of patients having potentially a uniform type of cardiac lesion, namely, hypertrophy of the left ventricle resulting from arterial hypertension. The attempt has further been made to elucidate the extraneous factors influencing the discrepancy in results obtained by the two standards and to test for the first time the validity of the conclusions offered in a small series of cases in which the actual heart weights were obtained at necropsy. The correlation with axis deviation in the electrocardiogram was also studied. Data obtained from Bainton's figures on persons without cardiac involvement have been utilized as a control series for comparison. The fact that the latter determinations were not made by us is considered desirable rather than otherwise, as the comparative results, embodying a possible multiplicity of subjective and objective error, should be applicable to the determinations made in any laboratory.

MATERIAL AND TECHNIC

Our series consisted of 79 patients, 50 of whom were women, with an average age of 56.6 years (youngest, 25 years; oldest, 79). The 29 men had an average age of 59 years (youngest, 22 years; oldest, 74). No attempt at selection was made beyond the assurance that each patient had a sustained systolic pressure of 150 mm. of mercury or more, and that congestive heart failure was not present, as it might introduce the complicating factor of ascites, with upward displacement of the diaphragm, hydropericardium, etc.

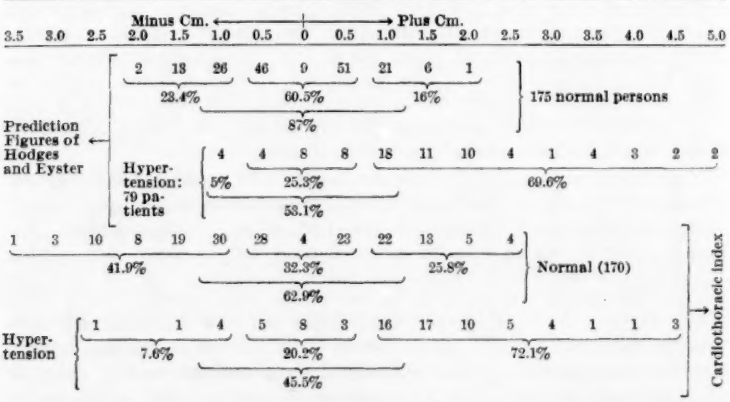
The orthodiagram was made with the patient in the standing position, breathing quietly. The fluoroscope used has a side arm which moves synchronously with both the tube and the screen in a vertical and in a horizontal plane. The cardiac silhouette was recorded by means of pencil dots on paper, corresponding in relative position with the black dot placed at the border of the heart and marking the point of emergence of the central rays from the tube. The tracings were made by three observers, and it was found that their determinations on the same patient varied as much as 0.5 cm. in the transverse cardiac measurement. This may be regarded as a fair estimate of the experimental error. No heart was considered enlarged unless its transverse diameter exceeded by 0.5 cm. the normal measurement as given by the standard under consideration.

RESULTS

In Persons Without Heart Disease.—Bainton found that in such persons the cardiothoracic index gave more of a "scatter," that is, placed more of these persons in a group with abnormally small or abnormally large hearts, than did the prediction figures of Hodges and Eyster. In table 1 the distribution by these two methods for patients without heart disease, as calculated from Bainton's data, and for our series of patients with potential cardiac enlargement, is indicated. The naught at the top indicates absolute coincidence of the predicted widths with the actual widths. The figures to the left indicate in centimeters the difference between the predicted and the actual transverse diameters of hearts smaller than normal by the two methods, and those to the right,

the difference in centimeters between the predicted and the actual transverse diameter of hearts larger than the predicted normal. It can be seen that by the method of Hodges and Eyster 41 (23.4 per cent ± 7.8) of 175 persons without heart disease had heart widths less by 1 cm., or more, than the predicted normal; that 106 (60.5 per cent ± 4.7) had cardiac widths within 0.5 cm. of the predicted normal, and that in the remaining 28 (16 per cent ± 7) the results fell in the group of abnormal cardiac enlargement. However, none of the subjects had an actual transverse diameter exceeding by 2 cm. the predicted normal width. Quite different results are secured by the cardiothoracic ratio, according to the figures obtained from Bainton's data. By that method 71 (41.9 per cent ±5.9) of his 170 patients had abnormally small hearts;

TABLE 1.—*Distribution of Size of Heart in Persons with and Without Potential Cardiac Enlargement*



55 (32.3 per cent ± 6.2) had heart widths within normal limits, and 44 (25.8 per cent ± 6.6) had cardiac widths exceeding by at least 1 cm. the predicted normal, of whom 5 had an enlargement of 2 cm. and 4 of 2.5 cm. The differences in distribution obtained by the two methods in persons without heart disease are statistically suggestive and, as Bainton showed, are not influenced by sex. Bainton did not attempt to unravel the factor or factors influencing the wide distribution obtained by the Danzer ratio, but concluded that the standard was of little value as a criterion of the normal size of a heart.

In Patients with Hypertension.—It would seem that the two standards, when applied to persons with hypertrophied hearts, should show the same differences in results obtaining in persons with normal hearts; that is, the prediction figures of Hodges and Eyster should give a

smaller scatter and a larger per cent of patients with abnormally great transverse cardiac diameters than would the cardiothoracic ratio. This of course postulates that the two series of patients are comparable in other respects—that there are no complicating extraneous factors. Table 1 shows that while in the series of patients with hypertension the magnitude of the scatter obtained by the two standards is of relatively the same degree as that present in the group with no cardiac involvement, the percentage of enlarged hearts (prediction figures of Hodges and Eyster, 69.6 per cent ± 6.1; Danzer ratio, 72.1 per cent ± 6) is approximately the same by both standards. The two methods show a surprising degree of correlation throughout. Hodges and Eyster's standard gave no enlargement in 24 (25.3 per cent ± 8.8) of 79 patients and the Danzer ratio, no enlargement in 22 (20.2 per cent ± 8.5). There was no enlargement by either method in 17 (21.5 per cent ± 9.6) of the patients. It is evident that there must be a factor, or factors, influencing the cardiothoracic ratio in our series of patients which was not operative in Bainton's series, for, if it were to be imagined that in his 71 patients with abnormally small hearts there developed a cardiac enlargement of 1 or 2 cm., this would place them in the group of persons with hearts of normal size instead of in the group with cardiac enlargement, while the Hodges and Eyster standard would presumably shift them well to the right in the diagram, thus maintaining the discrepancy in results obtained by the two standards.

In attempting to elucidate the factor, or factors, at work in our series, we first studied those cases in which the results obtained by the two standards were in disagreement as to the presence of cardiac enlargement. This occurred in 17 (20.5 per cent) of the 79 cases, exceeding the experimental error of the determination in 13 (16.4 per cent ± 3.2). The pertinent data in each instance are recorded in table 2. Of the 7 patients with significant cardiac enlargement by the Danzer ratio only, 6 were women. With one possible exception (case 18), all of the subjects were obese. Conversely, a tendency to underweight is apparent in the series of 5 patients having a significant cardiac enlargement by the Hodges and Eyster standard alone. This suggested a comparison of the two standards in the underweight and overweight persons in our series. To avoid the complicating factor of sex, women only were selected. The results are given in table 3, and for the sake of completeness the remaining cases in our series are listed in table 4. There were 17 women classifiable as obese. All but 1 had cardiac enlargement by the Danzer ratio, averaging for the group 1.8 cm. ± 0.03. Five had hearts of normal width, or less, as judged by the Hodges and Eyster standard, giving an average enlargement for the group of 0.7 cm. ± 0.02, the difference by the two methods averaging 1.1 cm. ± 0.1. In 9 underweight women a converse tendency was obvious, the prediction figures

TABLE 2.—*Enlargement of the Heart*

Case	Age	Sex	Height Ft.	Height In.	Weight, Lb.	Average Blood Pressure	Known Duration	One-Half Chest Diameter, Cm.	Actual Transverse Cardiac Diameter, Cm.	Enlargement, Cm.	Predicted Transverse Diameter, Cm.	Enlargement, Cm.
By Danzer Ratio Only												
18	80	F	5	0	135	165/120	?	10.0	11.3	1.3	11.6	...
31	71	M	5	11	184	170/ 80	2 to 3 yr.	11.2	13.5	2.3	13.6	...
32	58	F	5	2	220	150/ 85	?	12.0	12.9	0.9	14.3	...
60	64	F	5	2	174	210/120	?	10.7	12.2	1.5	12.7	...
69	73	M	6	6	173	155/ 80	?	12.0	12.2	0.2	12.9	...
98	50	F	5	7	150	150/100	12 yr.	11.3	11.5	0.2	11.5	...
12	59	F	5	6	174	180/110	10 yr.	9.9	12.0	2.1	12.5	...
29	52	F	5	5	165	180/ 90	?	11.0	11.9	0.9	12.2	...
40	61	F	5	5	213	210/110	?	12.0	13.5	1.5	14.1	...
73	67	M	5	10	176	185/110	7 mo.	12.0	13.1	1.1	13.2	...
By Prediction Figures Only												
85	44	M	5	10	169	180/110	4 yr.	15.0	14.3	...	12.8	1.5
43	22	M	5	9	139	150/100	1 yr.	12.6	12.1	...	11.5	1.6
86	66	F	5	7	100	190/ 90	2 yr.	12.5	12.0	...	10.1	1.9
92	43	M	6	1	206	180/110	?	14.5	14.5	...	14.0	0.5
97	43	F	5	0	115	155/125	?	12.5	11.2	...	10.4	0.8
16	60	F	5	3	106	170/ 90	?	10.2	10.1	...	10.3	0.2
94	55	F	5	8	177	155/ 90	?	13.5	13.0	...	12.4	0.6

TABLE 3.—*Size of Heart in Women*

Case	Age	Sex	Height Ft.	Height In.	Weight, Lb.	Average Blood Pressure	Known Duration	One-Half Chest Diameter, Cm.	Actual Transverse Cardiac Diameter, Cm.	Enlargement, Cm.	Predicted Transverse Diameter, Cm.	Enlargement, Cm.
Seventeen Obese Women												
35	49	F	5	4	195	200/130	8 yr.	11.7	14.9	3.2	13.2	1.7
37	45	F	5	3	165	180/110	9 mo.	11.7	13.1	1.4	12.2	0.9
40	61	F	5	5	213	210/110	?	12.0	13.5	1.5	14.1	—0.6
54	67	F	4	9	167	170/ 90	?	11.0	15.3	4.3	12.6	2.7
55	56	F	5	7	158	150/ 75	?	11.5	13.0	1.5	11.8	1.2
60	64	F	5	2	174	210/120	?	10.7	12.2	1.5	12.7	—0.5
76	59	F	5	10	195	160/110	10 yr.	12.0	14.1	2.1	13.1	1.0
77	41	F	5	11	177	155/115	3 yr.	12.5	13.8	1.3	12.2	1.6
90	55	F	5	0	158	200/100	8 yr.	10.5	13.5	3.0	12.2	1.3
94	55	F	5	8	177	155/ 90	?	13.5	13.0	—0.5	12.4	0.6
100	70	F	4	10	165	155/ 70	?	10.4	13.4	3.0	12.7	0.7
101	46	F	5	6	191	200/100	?	11.4	13.6	2.0	12.6	1.0
6	70	F	5	7	170	180/ 90	?	11.6	13.0	1.4	12.4	0.6
12	59	F	5	6	174	180/110	10 yr.	9.9	12.0	2.1	12.5	—0.5
29	52	F	5	5	165	180/ 90	?	11.0	11.9	0.9	12.2	—0.3
68	70	F	5	6	175	150/ 90	?	12.5	13.2	0.7	12.7	0.5
32	58	F	5	2	220	150/ 85	?	12.0	12.9	0.9	14.3	—1.4
Average										1.8 ± 0.03		0.7 ± 0.02
Nine Underweight Women												
16	60	F	5	3	106	170/ 90	?	10.2	10.1	—0.1	10.3	0.2
49	59	F	5	4	119	160/100	5 yr.	11.2	12.0	0.8	10.5	1.5
59	60	F	5	0	92	220/ 90	?	9.7	11.75	2.0	9.9	1.8
86	66	F	5	7	100	190/ 90	2 yr.	12.5	12.0	—0.5	10.1	2.4
97	43	F	5	0	115	155/125	?	12.5	11.2	—1.3	10.4	0.8
102	26	F	4	11	101	150/ 85	2 yr.	10.2	9.0	—1.2	9.9	—0.9
3	62	F	5	3	106	160/100	12 yr.	13.5	15.0	1.5	10.3	4.7
41	75	F	5	2	106	180/115	?	13.5	14.4	0.9	10.4	4.0
46	60	F	5	5	117	175/ 90	4 mo.	12.0	13.0	1.0	10.5	2.5
Average										0.34 ± 0.1		1.9 ± 0.1

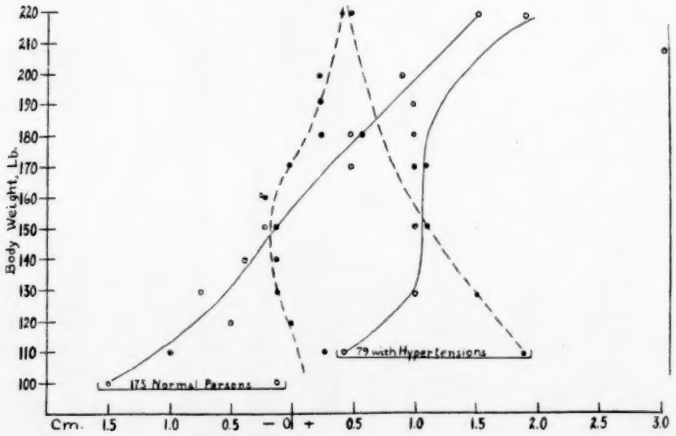
of Hodges and Eyster tending to show larger hearts (average, 1.9 cm. ± 0.1) than the Danzer ratio (average, 0.34 cm. ± 0.1). This makes it apparent that the large number of overweight persons in our series, as compared with Bainton's patients, who were preponderantly underweight or of normal weight, is the factor causing the discrepancy

TABLE 4.—*Size of Hearts of Subjects with Hypertension*

Case	Age	Sex	Height Ft.	Height In.	Weight, Lb.	Average Blood Pressure	Known Duration	One-Half Chest Diameter, Cm.	Actual Transverse Cardiac Diameter, Cm.	Enlargement, Cm.	Predicted Transverse Diameter, Cm.	Enlargement, Cm.
Twenty-Three Men												
1	54	M	5	8	174	200/110	1 yr.	13.0	14.0	1.0	13.1	0.9
2	54	M	5	7	165	210/130	3 yr.	15.0	16.5	1.5	12.9	3.6
4	74	M	6	2	173	170/ 85	?	16.5	18.0	2.0	13.1	5.9
5	45	M	6	0	200	210/140	2 yr.	14.2	18.0	3.8	13.8	4.2
15	56	M	5	8	145	190/110	8 yr.	12.7	13.0	0.3	12.1	0.9
19	37	M	5	5	135	165/120	5 mo.	12.1	11.6	−0.4	11.6	0.1
22	57	M	5	7	150	180/130	12 yr.	12.7	14.5	1.8	12.3	2.2
25	55	M	5	9	144	175/ 95	17 yr.	11.7	13.5	1.8	12.0	1.5
34	63	M	5	6	195	170/110	?	14.0	18.5	4.5	14.2	4.3
45	65	M	5	10	150	150/ 90	?	12.2	12.5	0.3	12.2	0.3
53	64	M	5	8	170	160/100	?	11.7	14.0	3.3	13.1	0.9
57	69	M	5	4	160	165/ 95	?	13.0	12.0	−1.0	12.0	−0.9
65	72	M	5	9	179	190/110	24 yr.	16.0	16.2	0.2	13.5	2.7
66	62	M	5	8	170	170/ 90	8 yr.	11.7	13.0	1.3	11.2	1.8
72	72	M	5	6	157	210/130	7 mo.	13.0	14.5	1.5	12.8	1.7
78	58	M	5	7	133	200/105	7 yr.	11.5	13.5	2.0	11.6	1.9
79	64	M	5	8	170	160/100	?	11.7	14.0	2.3	13.1	0.9
80	74	M	5	11	154	150/ 60	2 yr.	13.0	12.0	−1.0	12.5	−0.5
83	67	M	6	0	165	260/150	?	12.1	16.6	4.5	12.7	3.9
95	50	M	5	7	164	170/100	?	12.5	11.8	−0.7	12.8	−1.0
99	56	M	5	10	195	180/140	2 yr.	15.0	17.2	2.2	13.8	3.4
104	62	M	5	6	133	180/ 95	4 yr.	11.7	11.9	0.2	11.8	0.1
105	58	M	5	9	203	170/100	10 yr.	13.0	15.2	2.2	14.6	0.6
Twenty-Two Women												
11	79	F	5	6	124	230/ 90	10 yr.	13.0	14.5	1.5	10.8	3.7
20	78	F	5	1	134	210/ 80	18 yr.	11.5	12.5	1.0	11.4	1.1
26	46	F	5	8	125	170/120	4 yr.	10.5	10.8	0.3	10.5	0.3
28	56	F	5	6	143	190/110	10 yr.	11.0	11.8	0.8	11.3	0.5
30	41	F	5	0	121	140/ 85	10 yr.	11.3	12.7	1.5	10.7	2.0
42	68	F	5	2	148	230/130	15 yr.	11.7	13.5	1.8	11.7	1.8
51	72	F	5	2	121	160/ 85	?	10.2	12.8	2.6	10.9	1.9
56	60	F	5	2	130	180/100	?	11.0	11.0	0.0	11.1	−0.1
62	74	F	5	2	142	155/ 85	?	11.2	13.3	2.1	11.7	1.6
64	64	F	4	10	121	170/100	?	9.8	11.7	1.9	10.9	0.8
67	60	F	5	0	130	170/ 90	8 yr.	11.7	13.0	1.3	11.2	1.8
70	65	F	5	2	131	245/ 90	?	11.6	14.6	3.0	11.2	3.4
74	58	F	5	2	127	160/ 75	2 yr.	11.1	12.8	1.7	10.9	1.9
82	51	F	5	4	146	190/130	1 yr.	11.0	12.0	1.0	11.5	0.5
84	50	F	5	7	132	215/130	15 yr.	13.0	13.5	0.5	10.8	2.7
87	43	F	5	6	124	170/100	?	10.9	11.7	0.8	10.5	1.2
89	34	F	5	6	129	220/140	?	11.5	12.1	0.6	10.6	1.5
91	50	F	5	3	130	220/120	10 yr.	10.0	11.5	1.5	11.0	0.5
93	69	F	5	2	142	200/100	?	12.2	14.5	2.3	11.6	2.9
96	68	F	5	2	123	190/100	5 yr.	9.2	12.2	3.0	10.7	1.5
103	25	F	5	6	142	150/100	6 mo.	13.0	10.4	−2.6	10.9	−0.5
106	54	F	5	3	125	160/ 90	?	11.0	11.4	0.4	10.8	0.6

in results in the application of the standards in the two groups of subjects. The influence of body weight on the results obtained by the cardiothoracic ratio and by the prediction figures may be expressed graphically. In the chart the divergence in heart size from the predicted normal, expressed in centimeters, has been plotted against the body weight in pounds. The dots and circles representing an average value

for all persons at the weight indicated on the ordinate have been connected by smoothed curves. The data for persons without heart disease have been derived from Bainton's figures. There is a pronounced degree of correlation between the cardiothoracic index and the body weight in these persons, such that thin persons will have, according to this standard, hearts smaller than normal, whereas obese persons will have a cardiothoracic ratio placing them definitely in the group with cardiac enlargement. This correlation, as one might expect, is not as evident in the series of subjects with hypertension, but sufficiently definite to warrant the conclusion that the Danzer ratio is of little value in defining cardiac enlargement in thin persons.



Effect of body weight on the divergence from predicted normal transverse cardiac diameters. The broken line with the solid dots give the prediction figures and the unbroken line with the open circles the figures based on the cardiothoracic index.

That body weight, however, does not influence appreciably the criterion of normal by the prediction figures in the heart size of persons without heart disease, but apparently alters the results when applied to persons with hypertrophied hearts, is likewise evident. By this standard, thin persons with hypertension show the greatest cardiac enlargement, and obese persons, little or no enlargement. That this is not true is shown in table 5, in which are listed, in descending order of heart weight, the essential data, with the results obtained by the two standards under discussion, for 14 patients who came to autopsy and on whom orthodiagrams had been made a short time previously. Seven additional patients are listed in table 6, in whom the heart size was studied by means of a roentgen-ray plate made at a distance of 2 meters.

Attention is called to patient A. H., with a heart weight of 720 Gm., and to patient J. D., with a heart weight of 530 Gm. The standard of Hodges and Eyster failed to show enlargement. Both patients were obese. It may be concluded that the prediction figures are not trustworthy as a guide to abnormal heart size in the presence of obesity. From the data at hand, we are not prepared to say why this is so, unless it is that the high position of the diaphragm in obesity displaces the

TABLE 5.—*Weight of Hearts of Fourteen Patients Previously Studied by Orthodiagraphy*

Name	Sex	Age	Diagnosis	Weight, Lb.	Height Ft.	Height In.	Weight of Heart, Gm.	One-Half Chest Diameter, Cm.	Actual Transverse Cardiac Diameter by Orthodiagram, Cm.	Enlargement, Cm.	Predicted Transverse Diameter, Cm.	Enlargement, Cm.
J. E.	M	81	Hypertension, congestive heart failure	162	5	6	760	14.1	17.4	3.3	12.4	5.0
A. H.	M	71	Hypertension, angina pectoris, congestive heart failure	220	5	2	720	12.0	12.9	0.9	14.7	—1.8
A. C.	F	67	Hypertension, congestive heart failure	142	5	2	680	12.0	14.5	2.5	11.0	3.5
R. L.	M	54	Coronary sclerosis, angina pectoris	165	5	7	678	12.0	14.8	2.8	12.4	2.4
S. E.	M	44	Aortic regurgitation, carcinoma of pancreas	146	5	9	540	13.0	13.0	0.0	11.6	1.4
F. L.	M	75	Hypertension, coronary occlusion	156	5	6	530	13.5	15.7	2.2	12.2	3.5
A. B.	M	67	Coronary sclerosis, angina pectoris	120	5	5	530	11.0	13.8	2.8	10.9	2.9
J. D.	F	61	Hypertension, lobar pneumonia	213	5	5	530	12.0	13.5	1.5	13.6	—0.1
J. H.	M	50	Carcinoma of bronchus	175	6	1	470	15.0	12.7	—2.3	12.5	0.2
G. B.	M	72	Hypertension, coronary occlusion	170	5	8	440	13.2	13.2	0.0	12.6	0.6
S. R.	M	39	Malignant hypertension, uremia	144	5	10	430	12.7	15.7	3.0	11.5	4.2
S. D.	F	56	Primary pulmonary sclerosis	119	4	11	400	10.5	13.7	3.2	10.3	3.4
J. W.	M	64	Hypertension, aortic regurgitation, carcinoma of pancreas	159	5	7	340	13.0	15.7	2.7	12.2	3.5
I. S.	M	68	Hypertension, generalized arteriosclerosis	170	5	6	280	15.4	13.8	—1.6	12.6	1.2

cardiac apex outward, so that the greatest transverse cardiac diameter will bisect the apex tip itself instead of running through a point several centimeters above it on the left border, as in a normally placed heart. Likewise, the left ventricle may be rotated somewhat posteriorly. As a result of these two factors, superimposed left ventricular enlargement might not manifest itself by a detectable additional increase in the measurement as it would in a "drop" heart, for instance, in which the line of measurement passes through a point well up on the wall of the left ventricle which itself lies more anteriorly.

Correlation with Electrocardiographic Observations.—Electrocardiograms were made of 73 patients of our series. Forty-four (60.2 per cent) had a left axis deviation, 1 of whom (1.2 per cent) had no cardiac enlargement by the Danzer ratio. Four (9 per cent) had no enlargement by the prediction figures, while 5 (11.3 per cent) had a transverse cardiac diameter within the normal limits by both methods. One patient had a right axis deviation and a normal heart size by the Danzer ratio, but an enlargement of 2.7 cm. by the Hodges and Eyster standard. Of the remaining 28 patients with no axis deviation, the Danzer ratio and the prediction figures each showed abnormal enlargement in 3 patients, while 23 (82.1 per cent) of the group had enlarged hearts by both methods. The two standards, then, were in close agreement throughout, but both failed to correlate closely with the electrocardiographic observations. However, the data more truthfully demonstrate the well known fact that the electrocardiographic evidence of ventricular enlargement is often lacking in the presence of definite hypertrophy and/or dilatation. The correlation with the electrocardiogram is too indefinite to be of value in judging the efficacy of any cardiac measurement proposed as a guide to define the normal size of a heart.

TABLE 6.—*Weight of Hearts of Seven Patients Previously Studied by Roentgenography*

Name	Sex	Age	Diagnosis	Weight, Lb.	Height Ft.	Height In.	Weight of Heart, Gm.	One-Half Chest Diameter, Cm.	Actual Transverse Cardiac Diameter, Cm.	Enlargement, Cm.	Predicted Transverse Diameter, Cm.	Enlargement, Cm.
H. L.	F	30	Carcinoma of pancreas	124	5	2	200	12.0	11.0	—1.0	10.5	0.5
A. F.	F	53	Carcinoma of breast	100	5	0	210	12.1	12.4	0.3	9.8	2.6
M. G.	F	60	Carcinoma of pancreas	121	5	4	260	14.7	12.5	2.2	10.7	1.8
H. F.	M	54	Miliary tuberculosis	154	5	10	350	13.5	10.5	—3.0	12.3	—1.2
J. W.	M	44	Carcinoma of pleura	195	6	2	370	15.5	15.0	—0.5	13.6	—1.4
L. H.	F	54	Mitral stenosis	104	5	0	420	13.1	22.8	9.7	10.2	12.6
R. F.	M	48	Fibrosis of myocardium	180	5	9	570	16.0	19.0	3.0	13.3	5.7

SUMMARY AND CONCLUSIONS

The ratio of the transverse cardiac diameter to the internal diameter of the chest (Danzer ratio), as determined by orthodiagraphy, was compared with the predicted normal cardiac diameters of Hodges and Eyster in 175 persons without heart disease previously reported on and in 79 persons with arterial hypertension.

A direct correlation was found between the cardiothoracic ratio and the body weight in persons both with and without potential cardiac

enlargement, such that thin persons tended to have transverse cardiac diameters less than one half the internal diameter of the chest, and obese persons had cardiac diameters greater than this by more than the experimental error of the determination.

The predicted diameters of Hodges and Eyster, while approaching more closely the actual diameters found in persons without cardiac enlargement, failed to disclose the presence of left ventricular enlargement in obese persons, but were a satisfactory guide in normal or underweight subjects. It is suggested that this is not the fault of the standard per se, but is due to the failure of left ventricular enlargement, through mechanical causes, to manifest itself by a detectable increase in the transverse diameter of the heart in obesity.

Both methods failed to demonstrate enlargement in 20.2 per cent $\pm$ 8.5 of 79 persons who presumably had cardiac hypertrophy.

These conceptions regarding the efficacy of the two standards were corroborated by the study of a series verified at autopsy.

A comparison of the incidence of cardiac enlargement, as defined by these standards, with the occurrence of left axis deviation in the electrocardiogram showed that the correlation is too indefinite to be of value in judging the relative efficacy of such measurements proposed for the detection of cardiac enlargement.

Progress in Internal Medicine

DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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Into the subject "disease of metabolism" there now come not only diabetes, gout, obesity and a few other conditions involving chemical abnormalities of the body fluids, as formerly, but disturbances of the glands of internal secretion which affect the metabolic processes and disorders of nutrition which result from the lack in the food of adequate quantities of vitamins and other food factors. The desirability of the broader concept of the subject has been made apparent by the recent identification and separation, in many cases in pure crystalline form, of several of the hormones and vitamins. This has brought a fuller realization that the chemical reactions that constitute the metabolic process are dependent on the presence in suitable quantities of these specific catalysts. An instance in point is furnished by the recent rapid advancement of the knowledge of the physiology of the anterior lobe of the pituitary body. The new knowledge bears on carbohydrate metabolism and diabetes more decisively than anything that has been done in the field of carbohydrate metabolism since the isolation and discovery of insulin.

PROGRESS IN THE STUDY OF METABOLISM

HORMONES OF THE PITUITARY AND SUPRARENAL BODIES IN THE METABOLISM OF CARBOHYDRATE

That the metabolism of carbohydrate is in some way dependent on the function of the anterior lobe of the pituitary body, long suspected because of the relatively high incidence of acromegaly among patients suffering from diabetes, was dramatically revealed by the demonstrations of Houssay and his associates. After removing the pituitary body from frogs and from dogs, the removal of the pancreas was not followed by the usual degree of diabetes; indeed, some of the depancreatized animals showed no sugar in the urine and no hyperglycemia.

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Important information on the relationship between the pituitary body and carbohydrate metabolism is provided in a series of articles recently published by H. Lucke and his associates in Göttingen. The experiments were conducted on dogs.

The presence of a blood sugar-raising factor in extracts of the anterior lobe of the pituitary body, as indicated previously by the work of Houssay and Biasotti, Evans and others, was confirmed. Lucke preferred to call the factor "contra-insular hormone." The preparation he has used is a commercial preparation containing among other factors the blood sugar-raising principle (praephyson) supplied by the chemical firm Promonta of Hamburg. When given subcutaneously to normal dogs in doses from 5 to 10 cc. it produced a very slight elevation of the blood sugar; when given to dogs that had pancreatic diabetes it caused a marked increase of the hyperglycemia, and when given to dogs with pancreatic diabetes treated with insulin it produced hyperglycemia and increased the total excretion of dextrose. The effect, seemingly, was to counteract or to neutralize the action of insulin in lowering the level of the blood sugar.

In the regulation of the level of the blood sugar, the liver with its store of glycogen occupies the center of the stage as the effector organ. The pituitary hormone might reach the liver by way of the blood, either directly or indirectly; that is, it might act on the liver itself or on some gland of internal secretion, the secretion of which in turn would act on the liver. The thyroid gland and the suprarenal body might fall into this category of secondary order since both are included in the circuit of the blood and since the secretions of both have known effects on the store of glycogen of the liver. However, the peculiar anatomic relationship of the pituitary body to the central nervous system makes it necessary to consider a path of action which avoids the blood stream. The hormone might enter the cerebrospinal fluid through the stalk of the pituitary body and thereby stimulate the "sugar centers" in the brain stem or it might reach these centers by way of the blood. In either case the centers in question would be irritated, and nervous impulses could proceed by way of efferent sympathetic tracts and nerves to the primary or secondary effector organs involved. In this case the final effect, namely, glycogenolysis, likewise could be accomplished either directly, by the stimulation of the liver, or indirectly, by the stimulation of the thyroid gland or the suprarenal bodies. The possibility of nervous inhibition of the mechanism of the pancreas for the production of insulin, which would result in hyperglycemia, was not under consideration, because the hormone in the type of experiment conducted by Houssay is demonstrably active in the absence of the pancreas.

The possible intervention of the thyroid gland was an especially important question because of hormonal relationships previously recognized between the pituitary body and the thyroid gland and because of the well known influence of the hormone of the thyroid gland on the tolerance for dextrose of patients with diabetes. Lucke and his associates [1] found: (1) that the injection of a highly purified thyrotropic hormone did not elevate the blood sugar (this observation had previously been made by others); (2) that the effect of the blood sugar-raising hormone on the level of the blood sugar was much more immediate and of much greater intensity than the effect obtainable with thyroxine, and (3) that the effect of the blood sugar-raising hormone was not diminished by the previous removal of the thyroid gland. It was concluded that the blood sugar-raising hormone is wholly distinct from the thyrotropic hormone and in its action on the blood sugar does not involve the intermediation of the thyroid gland.

The possibility of intervention by the suprarenal glands was then investigated.[1c] These organs could be stimulated either by the blood sugar-raising hormone in the blood or indirectly by way of the central nervous system. The observations were as follows: 1. The hypersensitivity to insulin of suprarenalectomized animals was confirmed. Incidentally, attention is directed to the evidence reviewed by Grafe [2] which indicates a balanced relationship between the suprarenal glands and the pancreas, an increased supply of epinephrine stimulating greater release of insulin and vice versa. It has also been shown by LaBarre and Houssa [3] that the uncontrolled hyperglycemia of the dog with pancreatic diabetes is accompanied by a lowered secretion of epinephrine, that the administration of insulin under such circumstances stimulates the release of more epinephrine and that the administration of sugar again suppresses the activity of the suprarenal glands. According to LaBarre these effects are accomplished by the irritation of the sugar centers in the brain stem. The hypersensitivity to insulin which is observed in suprarenalectomized animals is attributed by Lucke to the loss of power to respond to the injection of insulin with the release of epinephrine.

2. The blood sugar-raising hormone in Lucke's experiments was without effect in raising the level of the blood sugar of suprarenalec-

1. Lucke, H.; Heydemann, E. R., and Duensing, F.: Untersuchungen über den Wirkungsmechanismus des kontrainsulären Hormons des Hypophysenvorderlappens: (*a*) I. Hypophysenvorderlappen, Schilddrüse und Kohlehydratstoffwechsel, Ztschr. f. d. ges. exper. Med. **91**:106, 1933; (*b*) II. Hypophysenvorderlappen, Nebenniereninsuffizienz und Kohlehydratstoffwechsel, ibid. **91**:483, 1933; (*c*) III. Hypophysenvorderlappen, Nebennierenentnervung und Kohlehydratstoffwechsel, ibid. **91**:492, 1933.

2. Grafe, E.: Ueber die Regulation der Insulinabgabe, Med. Klin. **28**:469 (April 1) 1932.

3. LaBarre, J., and Houssa, P.: Diabète et adrénalinesécrétion, Ann. de physiol. **8**:340, 1932.

tomized dogs, and it was concluded: that the activity of the anterior lobe of the pituitary body in carbohydrate metabolism depends on the presence of a functionally efficient suprarenal mechanism; that the path of action of the hormone must be by way of the suprarenal glands, and that the end-result, or the hyperglycemia, depends on a discharge of epinephrine.

There remained the problem as to how the suprarenal bodies were stimulated by the hormone in question, whether by way of the blood stream or by a primary irritation of the sugar centers in the brain stem. In the next experiments the nerve connections of the suprarenal glands of dogs were completely severed, which lowered the blood sugar level after fasting to 10 or 15 mg. per hundred cubic centimeters below the normal level and sensitized the animals to injections both of epinephrine and of insulin. Such animals were completely unaffected by injections of the blood sugar-raising hormone. The blood vessels to the suprarenal glands had been preserved, so it appears that the hormone in question does not affect the suprarenal glands through the blood stream but that its action is central, related to the suprarenal glands by nerve paths.

This does much to explain why animals deprived of suprarenal glands or with denervated suprarenal glands behave, with respect to their carbohydrate metabolism, like animals with insufficiency of the pituitary body, showing the same tendency to hypoglycemia and the same hypersensitiveness to insulin. In this connection stands the interesting observation of Viale[4] and of Long and Lukens.[5] The latter investigators, by making use of extracts of the cortex of suprarenal glands, were able to remove the suprarenal glands and the pancreas of cats, thereby obtaining animals like those of Houssay and Biasotti, with no glycosuria and relatively little hyperglycemia. It is evident that the suprarenal glands play a considerably larger rôle in carbohydrate metabolism than has been attributed to them heretofore, this being subject, however, to regulation by the anterior lobe of the pituitary body.

The next step taken by Lucke and his associates was to determine whether the blood sugar-raising hormone of the pituitary body reached the sugar centers in the brain stem by way of the blood stream or through the pituitary stalk and the cerebrospinal fluid. The active extract was injected into the cerebrospinal fluid through a suboccipital puncture. The procedure was almost painless and could be performed

4. Viale, Gaetano: Die Bedeutung der Nebennierenrinde für den Stoffwechsel der Kohlehydrate, Klin. Wchnschr. **12**:467, 1933.

5. Long, C. N. H., and Lukens, F. D. W.: Observations on Adrenalectomized, Depancreatized Animals, J. Clin. Investigation **13**:685 (July) 1934.

without resorting to narcosis and without constraining the animal. These are important considerations when the concentration of blood sugar is involved. It was found that when administered to normal dogs in this way, the hormone had an intense and prolonged effect, even in doses only one-tenth as large as those necessary to obtain results by subcutaneous or intravenous injection. In illustrative charts the blood sugar level is shown to rise almost immediately to a high point of about 70 mg. per hundred cubic centimeters above the basal level and to maintain a considerable elevation for as long as six hours. Control injections of pituitary extract, inactivated by heating, and of physiologic solution of sodium chloride produced relatively slight elevation of the blood sugar concentration. The conclusion was reached that the hormone normally is carried to the blood sugar centers and the brain stem by way of the cerebrospinal fluid. Also it was found that the hyperglycemia produced by suboccipital injection of the blood sugar-raising hormone could be checked immediately by blocking the sympathetic nervous system with a large intramuscular injection of ergotamine. Ergotamine in dogs ordinarily produces a slight depression of the blood sugar level of not over 20 mg. per hundred cubic centimeters. In the animals that had received the blood sugar-raising hormone by suboccipital injection, the blood sugar level of about 170 mg. per hundred cubic centimeters was almost instantly depressed below 100 mg., and after a lapse of two or three hours, as the effect of the ergotamine wore off, the blood sugar level again began to rise. The influence of general narcosis was similar. A narcotic was selected for the brain stem which has relatively little effect on the blood sugar. In a dog given 20 cc. of the blood sugar-raising hormone there developed unmistakable hyperglycemia, and the blood sugar level was promptly lowered by the intravenous injection of 0.4 Gm. of a barbituric acid derivative per kilogram of body weight. In another experiment a like dose of the barbituric acid derivative was given first, and after the blood sugar level had come to rest 5 cc. of the blood sugar-raising hormone was injected into the cerebrospinal fluid. This dose of the hormone was five times as large as would be required otherwise to cause marked hyperglycemia, yet the blood sugar level fell steadily for the following six hours. It was concluded that the functional efficiency of the brain and of the sympathetic nerve paths connecting the sugar centers and the suprarenal glands is essential for the exercise by the anterior lobe of the pituitary body of its regulative control of the blood sugar-raising activity of the suprarenal medulla. Of significance in this connection is the recent observation of Davis and his associates [6] that cats with experimental

6. Davis, Loyal: The Relation of the Hypophysis, Hypothalamus, and the Autonomic Nervous System to Carbohydrate Metabolism, Ann. Surg. **100**:654 (Oct.) 1934.

lesions accurately placed in the diencephalon withstand pancreatectomy without having severe diabetes develop. The pituitary body is not injured by the operation. The lesions, produced by means of the Horsley-Clark stereotoxic instrument, were bilateral and were situated in the tuber cinereum, "slightly rostro-dorso-lateral to the mammillary bodies at the level of the ventro medial hypothalamic nucleus." The cats had a high content of blood sugar, but could be maintained for long periods of time without exhibiting the symptoms usually observed after ablation of the pancreas. It is to be supposed that they would be resistant to suboccipital injections of the blood sugar-raising pituitary extracts, but so far as we know, this crucial experiment has not as yet been done.

In their next article Lucke and his associates [7] showed that the blood sugar-raising factor, if injected into the muscles, is secreted into the spinal fluid. From thirty to one hundred and twenty minutes after 20 cc. of the hormone was given to a dog by intramuscular injection, as little as 2 cc. of the spinal fluid of the dog injected into a normal rabbit was enough to provoke a marked elevation of the blood sugar level. The authors referred to the evidence compiled by Trendelenburg [8] which indicates that other pituitary hormones pass into the cerebrospinal fluid. The amount of blood sugar-raising hormone in the fluid is too small under normal conditions to permit its recognition, but the authors suggested that fluid containing demonstrable amounts of this hormone might be found in acromegalic patients with diabetes. This is to be watched for.

The general conclusions arrived at by Lucke are summarized as follows: Contrainsular hormone (the blood sugar-raising hormone) is formed in the anterior lobe of the pituitary body. The substance has not been identified chemically, but it possesses unmistakable biologic properties. It is certainly not identical with the gonadotropic and thyrotropic hormones, but thus far it has not been separated from the growth hormone. It is distinguished from the pituitary hormone of fat metabolism of Anselmino and Hoffmann [9] by filtration. Like the Anselmino hormone it promotes an increase of acetone in the blood and is found in association with the gonad-stimulating hormone, but unlike the Anselmino hormone it is not ultrafiltrable. The blood sugar-raising factor of the pituitary body is secreted into the cerebrospinal fluid and under special conditions can be demonstrated biologically in the fluid.

7. Lucke, H., and Hahndel, H.: Untersuchungen über den Wirkungsmechanismus des kontrainsulären Hormons des Hypophysenvorderlappens: VI. Die Möglichkeit eines biologischen Nachweis des Kontrainsulären Hormons im Liquor cerebrospinalis, Ztschr. f. d. ges. exper. Med. **91**:704, 1933.

8. Trendelenburg, Paul: Die Hormone; ihre Physiologie und Pharmakologie: Vol. 1. Keimdrüsen. Hypophyse. Nebennieren, Berlin, Julius Springer, 1929.

9. Anselmino, K. J., and Hoffmann, Friedrich: Die Ursachen des Icterus Neonatorum, Klin. Wchnschr. **10**:97 (Jan. 17) 1931.

Its immediate action is on the sugar centers of the brain stem. Consequently, it is ineffective when these centers are neutralized by pharmaceutic means (or destroyed by experimental lesions?). In turn, under the influence of the hormone, the brain centers activate the suprarenal glands, the stimulation passing from the centers to the suprarenal glands by way of the sympathetic nervous system. For this reason the action of the pituitary hormone is interrupted by pharmacologic or mechanical inhibition of the respective sympathetic nerve fibers as well as by extirpation of the suprarenal glands. The thyroid gland is not involved. The end-effect, elevation of the level of the blood sugar, is a result of the release of epinephrine, but the anterior lobe of the pituitary body and not the suprarenal glands is the regulator.

The possible application of these observations to the treatment of diabetes is discussed by Lucke [10] in a later article. The surgical removal of one suprarenal body is followed by no evidence of suprarenal insufficiency and therefore can be of no significance therapeutically. Bilateral suprarenalectomy is out of the question because of its fatal consequences. Rupp [11] demonstrated in 1925 that section of the splanchnic nerves in animals exaggerated the effect of insulin in lowering the level of blood sugar. Cesa-Bianchi and Moretti [12] observed some depression of the blood sugar concentration of diabetic patients after treatment with ergotamine, but the dose of ergotamine necessary for this is in the range of toxicity. Ciminata [13] in 1928 claimed to have cured pancreatic diabetes in animals by sectioning the suprarenal nerves. This was disputed by Nothmann,[14] who pointed out that the protocols presented by Ciminata indicated an incomplete pancreatectomy. Nevertheless, Ciminata has at least demonstrated the favorable influence of denervation of the suprarenal glands in a condition of partial diabetes. An improvement in the tolerance for dextrose after denervation of the suprarenal glands was observed by de Takáts and Cuthbert,[15] after resection of the celiac ganglion in dogs. Since then, de Takáts and Fenn [16] have described the clinical results of bilateral splanchnic section

10. Lucke, Hans: Stellt die Entnervung der Nebennieren eine aussichtsvolle Diabetesbehandlung dar? Ztschr. f. klin. Med. **125**:361, 1933.

11. Rupp, F.: Ueber den Einfluss des Nervensystems auf den Zuckergehalt des Blutes, Ztschr. f. d. ges. exper. Med. **44**:476, 1924-1925.

12. Cesa-Bianchi and Moretti, quoted by Lucke.[10]

13. Ciminata, A.: Einfluss der Durchschneidung der Nebennieren auf den Diabetes mellitus, Klin. Wchnschr. **11**:150 (Jan. 23) 1932.

14. Nothmann, M.: Einfluss der Durchschneidung der Nebennieren-Nerven auf den Diabetes mellitus, Klin. Wchnschr. **11**:774 (April 30) 1932.

15. de Takáts, G., and Cuthbert, F. P.: The Effect of Coeliac Ganglionectomy on the Sugar Tolerance of Dogs, Am. J. Physiol. **102**:614 (Dec.) 1932.

16. de Takáts, G., and Fenn, G. K.: Bilateral Splanchnic Nerve Section in Juvenile Diabetes, Ann. Int. Med. **7**:422 (Oct.) 1933.

in cases of diabetes in man. The results are encouraging in that much less insulin is necessary after the operation, but the procedure does not constitute a cure of the metabolic disorder nor does it permit the patient to do without insulin. The experiments of de Takáts and those of J. M. Donald [17] are significant and support Lucke's conclusions that the impulse between the sugar centers in the brain stem and the liver is transmitted through the suprarenal glands. Neither de Takáts nor Donald was able to detect any influence on the tolerance for dextrose from procedures which effected the denervation of the liver alone.

The bearing of this complex physiology on the conception of the pathologic physiology of diabetes and on the treatment of spontaneous diabetes in man is not entirely evident. A classic experiment of Claude Bernard established the significance of a "sugar center" in the medulla, and subsequent investigation has demonstrated other centers concerned with carbohydrate metabolism located in the diencephalon. The not infrequent occurrence of glycosuria following fracture of the base of the skull has long been a matter of common knowledge to physicians. This and the less frequent glycosuria accompanying tumor and other pathologic lesions of the brain has been attributed to irritation of these centers. However, the glycosuria which accompanies such lesions has in almost all cases been transitory and mild, differing markedly in these respects from diabetes mellitus. The frequency of association of acromegaly and diabetes is not as impressive as might be supposed from some reports. Occasionally authors place it as high as 40 per cent, but in other series it has not been over 7 per cent. A positive reaction to the test of sugar tolerance can sometimes be obtained in persons with no glycosuria, and, on the other hand, occasional cases have been described by Oppenheimer [18] and Lichtwitz [19] in which spontaneous recovery occurred from diabetes which was so severe as to threaten death in coma. Von Noorden [20] considered this question among others in a recent general lecture on diabetes. He admitted that diabetes associated with acromegaly is characterized by fluctuations in severity that seem not to be influenced by treatment, but he considered that the existence of a type of diabetes caused by a pituitary disturbance which is independent of disease or of abnormality of the insular system is highly improbable. It is necessary in connection with recent interest

17. Donald, J. M.: Studies on Carbohydrate Metabolism Following Denervation of the Liver, Am. J. Physiol. **98**:605 (Nov.) 1931.

18. Oppenheimer, Albert: Ueber das Wesen der Zuckerkrankheit bei Akromegalie, Klin. Wchnschr. **9**:17 (Jan. 4) 1930.

19. Lichtwitz, L.: Hypophysäre Symptome und Hypophysenkrankheiten, Verhandl d. deutsch. Gesellsch. f. inn. Med. **42**:35, 1930.

20. von Noorden, Carl: Zur funktionellen Pathologie und Therapie der Zuckerkrankheit, Med. Klin. **29**:39 (Jan. 6) 1933.

in the pituitary body to recall the studies of Borchardt [21] of Königsberg who, in 1908, produced glycosuria and hyperglycemia by the injection of crude extract of the pituitary body of the horse and of man. Borchardt thought it possible that a continuous excessive secretion of a product of the pituitary body might produce lasting diabetes in the active stage of acromegaly and that arrest of the excessive secretion, as a result of later degeneration of the pituitary tumor, might account for the absence of urinary sugar in many patients with acromegaly.

There is no evidence to incriminate the pituitary body in cases of diabetes unassociated with acromegaly. E. J. Kraus [22] demonstrated changes in the pituitary body in the large majority of persons with diabetes, especially in younger persons, but there is nothing in his work to indicate that the lesion of the pituitary body was primary. Almost all the cases of young persons with diabetes which come to necropsy are cases of uncontrolled diabetes in which death resulted from diabetic acidosis. That the pituitary body under such circumstances should show evidence of degeneration cannot be accepted as evidence of primary disease of this organ.

Whether the course of diabetes can be modified by measures directed toward suppressing the activity of the pituitary body remains to be seen. Hutton [23] claimed to have obtained favorable therapeutic effects by the intensive roentgen irradiation of the pituitary body, but thus far no confirmatory observations have come to our attention. Another means of suppressing the activity of the anterior lobe of the pituitary body may be to administer large amounts of so-called female sex hormone. There seem to have been no reports of this in the clinical literature on diabetes, but Barnes and his associates,[24] who were among those to confirm the original experiments of Houssay and Biasotti, found that the administration of estrogenic substance to normal female dogs prevented all but mild glycosuria after pancreatectomy. When the injections of the estrogenic substance were discontinued the animals became severely diabetic; the resumption of the injections caused a reduction in the glycosuria. The authors issued a warning against the clinical application of this procedure until more

21. Borchardt, L.: Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, Ztschr. f. klin. Med. **66**:332, 1908.

22. Kraus, E. J.: Ueber Beziehungen der chromophilen Zellen der Hypophyse zum Kohlehydrat-, Fett- und Cholesterinstoffwechsel, Med. Klin. **29**:449 (March 31) 1933.

23. Hutton, J. H.: Diabetes Mellitus and Essential Hypertension: A Theory as to Their Etiology and Treatment, Illinois M. J. **64**:539 (Dec.) 1933.

24. Regan, J. F., and Barnes, B. O.: The Relation of the Hypophysis to Experimental Diabetes, Science **77**:214 (Feb. 24) 1933. Barnes, B. O.; Regan, J. F., and Nelson, W. O.: Improvement in Experimental Diabetes Following the Administration of Amniotin, J. A. M. A. **101**:926 (Sept. 16) 1933.

of the effects of the estrogenic factor are known. Complete suppression of the pituitary body might be followed by the atrophy of other organs. This is especially true of the suprarenal cortex, which undergoes an involution when the pituitary body is removed.

HEREDITY IN DIABETES

Many students of metabolism, while impressed with the frequency of the incidence of diabetes in the parents and the siblings of diabetic patients, have been wary of accepting mendelian interpretations—and very properly so. The data are not of the sort that permit a forthright decision. The statistical analysis of such data must depend, for instance, on the age of the nondiabetic as well as of the diabetic members of the families examined, and few clinical records contain this information. An ideal genealogy would be that of a family in which every member had lived beyond the ninth decade, so that a complete opportunity for the expression of the disease had been given to every member. Pincus and White, from the laboratory of general physiology, Harvard University, and the Joslin Diabetic Unit of the New England Deaconess Hospital, respectively, have collected data which are undoubtedly superior to anything that has appeared before. The material consists of detailed family histories of 523 diabetic patients and control histories of a nondiabetic group, together with the analysis of a large group of cases from the clinic of Dr. Joslin and from other clinics. Also, twenty-three families were studied in which both parents had diabetes. Diabetes occurred ten times more frequently among the brothers and sisters of the persons with diabetes than it did among the control population, and the investigators concluded that the occurrence of diabetes among children of diabetic parents is in accord with the hypothesis that the potentiality for developing diabetes was inherited as a simple mendelian recessive. If this was correct, they expected to predict not only the number of offspring with diabetes in the twenty-three conjugal families but also the age at onset. This was accomplished. Their conclusions mean that when a diabetic person marries a diabetic person all the children are predestined to have diabetes; it will develop in 0.2 per cent in the first decade, in 3 per cent in the second, in 5 per cent in the third, in 10 per cent in the fourth, in 20 per cent in the fifth, in 30 per cent in the sixth, in 50 per cent in the seventh and in 60 per cent in the eighth. If a person with diabetes marries a carrier of potentiality to acquire diabetes one half of the offspring are predestined to have diabetes. If a carrier marries a carrier, one fourth of the children are predestined to have diabetes. But if a person with diabetes marries a person who has not diabetes, none of the children are predestined to have diabetes. Diabetic patients who wish to marry and have children

may do so provided the marriage is to a person who neither has diabetes himself nor is a carrier of the potentiality. Conversely, the marriage of two diabetic persons, which would be sure to result in diabetic children, must be avoided. The prevalence of diabetes in the Jewish race is probably accounted for on this basis. Not only must one train diabetic children to marry into families in which there is no trace of diabetes but, as pointed out by Pincus and White, one must also carry this instruction to the children of diabetic parents, for they represent true and insidious carriers of the disease. A study by L. R. Grote [25] led to similar conclusions. A diabetic taint was found in the families of 40 per cent of 457 persons with diabetes, and he recommended that the marriage of two persons with diabetes be forbidden by law or be permitted only on the condition that both parties be sterilized. The right to marry should be questioned if both come from diabetic families, even though neither actually has diabetes, and the permissibility of marriage between a diabetic person and a nondiabetic person should depend on the proof of the absence of diabetes in three generations of the blood relatives of the latter.

SYMPOSIUM OF THE NEW YORK ACADEMY OF MEDICINE

An unusually instructive series of lectures on the disorders of metabolism was held by the New York Academy of Medicine from Oct. 23 to Nov. 3, 1933. The total exchange of energy was the subject of a lecture by DuBois.[26] He referred therein to the relationship of the velocity of the blood flow and cardiac output to the total metabolism. The whole problem of the management of heart disease, as revealed with particular clarity by the studies of Blumgart,[27] Weiss and others, is linked with the demands of total metabolism, and the required cardiac output, with the capacity of the heart to meet the need. In conditions of congestive heart failure and coincidental pathologic states without clinical evidence of thyroid toxicity, benefit may be derived from lowering the basal metabolic level by total ablation of the thyroid gland.

The patient who was first subjected to this procedure was presented at the meeting by Dr. Blumgart and his associates. Previously bed-

25. Grote, L. R.: Ueber die Vererblichkeit der Zuckerkrankheit, Med. Klin. **1**:185 (Feb. 9) 1934.

26. DuBois, E. F.: Total Energy Exchange in Relation to Clinical Medicine, Bull. New York Acad. Med. **9**:680 (Dec.) 1933.

27. Blumgart, H. L.; Riseman, J. E. F.; Davis, David, and Berlin, D. D.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: III. The Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, Arch. Int. Med. **52**:165 (Aug.) 1933. Blumgart, H. L.; Levine, S. A., and Berlin, D. D.: Congestive Heart Failure and Angina Pectoris. The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity, Arch. Int. Med. **51**:866 (June) 1933.

ridden, he was engaged in the exhibition hall in running the moving picture demonstration of the technic of the operation. He required a very small dose of thyroid extract to maintain his metabolic rate at the upper limit of the myxedema zone. The procedure is still on trial and is not to be hastily recommended. The surgical mortality is very high. The operation required involves the risk of injury to the recurrent nerves and to the parathyroid bodies. Lourie,[28] fearful about the death rate if the operation becomes popular among less skilful surgeons, begs for a truce of at least two years in order to give time for a better evaluation of the results already obtained. He regards the results as being very questionable. A recent paper [29] from the Mayo Clinic relates the case of a man with diabetes mellitus who was treated by total thyroidectomy. The outcome, while of importance theoretically by showing that less insulin is required to support the carbohydrate metabolism when the basal metabolic rate is lowered, does not encourage the repetition of the operation for diabetes. The patient complained that sensitiveness to cold and the lack of endurance were so disturbing that the advantage of improved tolerance was not appreciated.

One of the outstanding features of diabetes consists in alterations of the water metabolism as indicated by the symptoms of polydipsia and polyuria. Himwich [30] reported the production of a temperature of 104 F. (40 C.) in diabetic dogs by withholding insulin and water. The fever was attributed to anhydremia. Coincident anoxemia was encountered in the muscles, with a resulting rise of the lactic acid content of the blood and changes in the electrocardiogram similar to those observed when there is an insufficient supply of oxygen to the heart. Starr and Fitz in 1924 and other writers subsequently have commented on the presence of an organic acid not comprised in the group of acetone bodies in the urine of patients with diabetic acidosis. The observations of Himwich revealed that the unknown acid is lactic acid. In the twenty-four hour specimens of urine of one of his dogs, the amount of lactic acid was 1,885 mg.

The lecture on acidosis and alkalosis by Van Slyke [31] is recommended for reading by those who have had difficulty in following the scientific literature on the subject. Excess of carbonic acid, deficit of carbonic acid, excess of alkali and deficit of alkali, their causes,

28. Lourie, O. R.: Is Total Thyroidectomy Rational as a Method of Treatment? Canad. M. A. J. **31**:502 (Nov.) 1934.

29. Wilder, R. M.; Foster, R. F., and Pemberton, J. deJ.: Total Thyroidectomy in Diabetes Mellitus, Endocrinology **18**:455 (July-Aug.) 1934.

30. Himwich, H. E.: The Metabolism of Fever, with Special Reference to Diabetic Hyperpyrexia, Bull. New York Acad. Med. **10**:16 (Jan.) 1934.

31. Van Slyke, D. D.: Acidosis and Alkalosis, Bull. New York Acad. Med. **10**:103 (March) 1934.

significance and rational treatment are discussed with extraordinary lucidity and without too great a demand on the reader's acquaintance with gas laws, equilibrations and dissociation curves.

Diabetes was thoroughly considered in a round table conference engaged in by Woodyatt, White, Scott, Mosenthal and Geyelin.[32] The papers should be read by all physicians engaged in the treatment of the disease; only a few of the high points can be mentioned here. Woodyatt, in reviewing dietary trends, commented on the fact that an occasional diabetic patient may have carbohydrate added to his diet with actual advantage to his tolerance. The metabolic data in one such case were presented. It was pointed out that similar observations were probably the basis for the von Noorden "oatmeal cure," the Mossé "potato cure" and other carbohydrate "cures." Unfortunately, as von Noorden wrote, "there are relatively few cases in which the results are so surprisingly favorable." In 1911 Klemperer appears to have demonstrated that analogous results could be produced by the administration of dextrose, but during the early stages in Woodyatt's experiment the patient was excreting dextrose, and there was at all times an excess of dextrose in the body. Although several hypotheses have been advanced to explain the phenomenon, it still presents an interesting problem for further investigation.

In this connection Geyelin reported 40 cases of diabetes in which the patients had been treated with insulin and diets high in fat and low in carbohydrate. They were subsequently given diets containing "normal" proportions of carbohydrate, protein and fat. Twenty-six of them had values for blood cholesterol higher than normal before the change in diet was made. In Geyelin's diets the proportion of carbohydrate to fat has been approximately $3\frac{1}{2}:1$, but a few patients were found whose values for blood cholesterol did not return to normal limits until the proportion of carbohydrate to fat reached 4:1. It seemed to Woodyatt, as it has to many other physicians interested in this field, that the most effective diet is one in which the patient obtains the necessary number of calories with the lowest possible dose of insulin. The general conclusion has been that while individual patients may do with relatively small doses of insulin on a diet containing 300 Gm. or more of carbohydrate, the majority of these patients find insulin economy when more of their calories are provided by fat.

Scott issued a timely warning against "giving too much insulin to our older diabetic patients." Nathanson, of the University of Minnesota, showed by necropsy in 100 cases of diabetes that "the incidence of coronary sclerosis is approximately six and one-half times greater in

32. Woodyatt, R. T.; White, Priscilla; Scott, J. R.; Mosenthal, H. O., and Geyelin, H. R.: Round Table Conference on Diabetes Mellitus, Bull. New York Acad. Med. **10**:335 (June) 1934.

diabetics than in nondiabetics." As it is known that a heart diseased by arteriosclerosis of its coronary arteries needs more dextrose to function properly than does the normal heart, it is wise to treat diabetic patients over 50 years of age as potential subjects for heart disease and to insure an adequate level of blood sugar at all times. In other words, while 100 mg. per hundred cubic centimeters of whole blood is an ample concentration of blood sugar for normal persons with a normal heart, or even for young diabetic patients with a normal heart, this may not be ample for older patients with diabetes.

FACTORS INFLUENCING THE ACTIVITY OF INSULIN

Boller, Uiberrak and Falta [33] have recently reported the result of extensive studies bearing on the problem of resistance to insulin. They demonstrated that the transfusion of 300 cc. of blood from a normal donor who had recently received a breakfast containing carbohydrate produced in a diabetic recipient who was sensitive to insulin a sharp, if temporary, depression of the blood sugar level. A similar result was obtained with blood from a diabetic donor sensitive to insulin who had received an injection of from 20 to 40 units of insulin. The amount of insulin contained in the 300 cc. of transfused blood was estimated as about 1.3 units. Diabetic recipients of such transfusions who are resistant to insulin give a negative response, as would be anticipated, but, what is more important, the blood from diabetic donors who are resistant to insulin and who have received an injection of 40 units of insulin fails to produce any effect on diabetic recipients who are sensitive to insulin.

It had previously been shown by the authors that the insulin injected into patients who were resistant to insulin was not lost by excretion in the urine. It might be assumed that the injected insulin in such cases was anchored by the tissues, but if so it is not apparent why it should be inactive. Therefore, the authors were led to the opinion that one or several antibodies are present in patients who are resistant to insulin and that these are responsible for the relative inactivity of injected insulin.

The technic of these transfusions was not described in full, but the authors said that no anticoagulants were used and that precautions were taken to avoid disturbing the blood sugar level of the recipients by painful or psychic stimuli. By patients who are sensitive to insulin the authors referred to those who, like depancreated dogs, (1) require a relatively small dose of insulin, (2) are thrown into hypoglycemic shock if more than enough insulin is given to equalize the dextrose

33. Boller, R.; Uiberrak, K., and Falta, W.: Ueber die humerale Natur der Insulinresistenz, Wien. Arch. f. inn. Med. **25**:25 (June 20) 1934.

available or if insulin is given without food, the "Radoslov procedure," and (3) excrete a large amount of dextrose in the urine when insulin medication is discontinued. The patients who are resistant to insulin and who are said by the authors to be encountered in rather large numbers (1) require excessively large doses of insulin, (2) can be given extra insulin, that is, insulin over and above the amount necessary to make the urine sugar-free, without showing the symptoms of insulin shock and (3) excrete relatively little dextrose when insulin medication is discontinued. This differentiation of diabetic patients into "insulin-sensitive" and "insulin-resistant" types is described elsewhere by Falta.[34]

Also bearing on the question of the inactivation of insulin by the blood is a study by Bürger and Kohl.[35] It had been demonstrated by them previously that insulin when injected into an animal after clamping off the arteries to the principal masses of muscles had very little effect on lowering the blood sugar level and that if after an hour the clamps were removed so that blood reached the muscles there still was no lowering of the blood sugar level, although a second injection of insulin produced a characteristic effect indicating that the muscles were still intact. The observation led to the supposition that insulin was destroyed by the blood, and in the present study this was found to be the case. Insulin in crystalline form lost its activity when added to blood in vitro and incubated at 37 C. (98.6 F.) for from one to several hours. The same change occurred in a similar experiment with serum. That the neutralizing effect of the blood serum was attributable to an enzyme-like factor was suggested by the fact that the "inactivation" of the blood or serum by heating destroyed its ability to neutralize insulin. It was further observed that the blood of patients with lymphatic or myeloid leukemia possessed a greater neutralizing effect than did the blood from patients with no leukemia and that blood taken from the same leukemic patients after the leukocyte count had been reduced by roentgen irradiation behaved no differently than blood from normal persons. The bearing of this on the relative resistance to insulin of diabetic patients with leukocytosis is apparent. We are unaware of reports on the resistance to insulin in cases of diabetes complicated by leukemia.

Bearing on this matter of the activity of insulin are the astonishing results of experiments on the influence of magnesium in carbohydrate metabolism, as reported by Hans Franke[36] of Breslau. It was found

34. Falta, W.: Insulin und Diabetes mellitus, Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffwechselkr. **11**:124 (Oct.) 1932.

35. Bürger, M., and Kohl, H.: Ueber kristallinisches Insulin: V. Ueber Inaktivierung des Insulins durch Blut, Arch. f. exper. Path. **174**:130, 1933.

36. Franke, Hans: Magnesium und Kohlehydratstoffwechsel, Arch. f. exper. Path. **174**:727, 1934.

that the intravenous injection, within an hour, of a solution of magnesium chloride or magnesium gluconate, in concentration such that the total supply represented 100 mg. of magnesium, caused an increase in the glycogen of the liver to three or four times the amount normally present and no decrease, but a slight increase, in the glycogen of the muscles. Control injections of sodium chloride and of "phosphate solution" had no such effect, and injections of calcium chloride caused only a slight increase in the glycogen of the liver. When magnesium was injected together with epinephrine, the usual influence of epinephrine on both the muscle and the liver was missed, and the quantity of glycogen was increased to three or four times the normal amount both in the liver and in the muscle. The magnesium salts exerted similar effects when given by mouth.

EXERCISE AND THE BLOOD SUGAR LEVEL

It is commonly believed that exercise reduces the blood sugar level of diabetic patients. Richardson [37] determined the effect of a standard form of exercise in 61 cases of diabetes, finding that in mild cases, with a blood sugar level after fasting between a normal value and 175 mg. per hundred cubic centimeters, a marked lowering of the blood sugar level was produced, but that in severe cases with the level ranging from 175 to 300 mg., a progressively marked elevation resulted. In the severe cases of diabetes the intravenous injection of 0.1 unit of insulin when given before a period of rest was without marked effect on the blood sugar value but when given before a period of exercise caused a marked drop in the blood sugar values. The comparison of the values for the mild and those for the severe cases suggests that in the former the difficulty was one of an inadequate, or inadequately available, glycogen reserve of the muscles and liver and that in the latter it was one of more or less complete inability to convert the dextrose of the blood to the needs of the tissues.

PURINE METABOLISM AND GOUT [38]

While evidences of an abnormal purine metabolism have been regarded as the most prominent feature of gout, modern writers more and more are coming to view the abnormalities of purine observed in gout as the result rather than the cause of the disease and as of secondary importance. Thus Knaggs,[39] after a study of the Strangeways collection

37. Richardson, Russell: Factors Determining the Effect of Exercise on Blood Sugar in the Diabetic, J. Clin. Investigation **13**:949 (Nov.) 1934.

38. Dr. P. S. Hench supplied the material for this section.

39. Knaggs, R. L.: A Report on the Strangeways Collection of Rheumatoid Joints in the Museum of the Royal College of Surgeons, Brit. J. Surg. **20**:113 (July) 1932.

of specimens of diseased joints, suggested that the deposition of urates in the joints is relatively unimportant and a minor effect of metabolic changes in which other toxic bodies are produced in addition to urates. Gout, according to Knaggs, is closely akin to the rheumatoid infections. In the Strangeways collection nearly every specimen presents hypertrophic bony phenomena which apparently are followed by degenerative changes similar to those seen in atrophic (rheumatoid) arthritis. The characteristic pathologic changes are illustrated in Knaggs' article by several excellent photomicrographs by Rodman. Watson [40] has accepted Llewellyn's idea that the cause of gout is cellular sensitization, in other words, an allergic phenomenon, the exciting factor being endogenous or exogenous proteins of pathologic and biochemical origin, the predisposing factor being heredity.

The uric acid content of the blood in diabetes has received relatively little attention. Yet Ricci [41] noted that when diabetic subjects fasted the uric acid content of the blood was high in those to whom insulin was not given and normal in those to whom insulin was given and that, furthermore, the elevation of the uric acid content of the blood following a meal high in purine was more prolonged in persons with diabetes than it was in normal controls. Bertram [42] found that the uric acid content of the blood is greatly elevated in the absence of an increase in nonprotein nitrogen in patients with diabetes in a stage preceding coma or in coma. Quick reported that aceto-acetic acid administered orally to normal persons determines the output of uric acid and concluded that the retention of uric acid in diabetes, as in fasting and after a meal high in fat, is to be explained by the action of organic acids. Lactic acid, when given orally or when produced by strenuous exercise, by chloroform poisoning or by an excess of sodium bicarbonate, and benzoic acid, phenylacetic acid and numerous other aromatic acids, decreases the excretion of uric acid, and Quick [11] proposed the theory that the excretion of uric acid requires an adequate supply of antiketogenic material. In harmony with these observations is the report of Lockie and Hubbard [43] that they were able to precipitate an attack of gout in predisposed subjects by feeding a diet high in fat and that they could cause an attack to subside by giving a diet rich in carbo-

40. Watson, A. G.: Common Maladies and Their Treatment: Gout, Prescriber **27**:203 (June) 1933.

41. Ricci, quoted by Quick, A. J.: A New Concept of the Significance of Uric Acid in Clinical Medicine, M. Clin. North America **17**:1326 (March) 1934.

42. Bertram, quoted by Quick, A. J.: A New Concept of the Significance of Uric Acid in Clinical Medicine, M. Clin. North America **17**:1326 (March) 1934.

43. Lockie, L. M., and Hubbard, R. S., in Hench, P. S.: Proceedings of the First Annual Meeting of the American Association for the Study and Control of Rheumatic Diseases: Third Conference on Rheumatic Diseases, J. A. M. A. **103**:1883 (Dec. 15) 1934.

hydrate. The scarcity of gout among patients with diabetes, as noted by Joslin [44] and others, and the infrequency of attacks of arthritis in our experience with patients living on ketogenic diets are difficult to reconcile with these observations.

Since the advent of the newer methods of treatment for pernicious anemia, the occasional precipitation of an attack of gout by the administration of liver extract and a preparation of desiccated hog stomach has been reported. Sears [45] discussed (1) the observation by Riddle of an increase of the uric acid in the blood twenty-four hours after starting treatment with liver extract; (2) 2 cases of gout attributed by Spence to the excessive ingestion of liver, and (3) a case observed by himself, in which a typical first attack of gout occurred on the thirty-sixth day of treatment with a preparation of desiccated hog stomach.

The classic treatment of gout by the restriction of purine, hot and cold applications, rest and preparations of colchicum and cinchophen continues unchallenged and has remained unchanged for years. When one recalls that aside from the use of cinchophen, introduced in 1908, there has been no major change in the therapy of gout since the introduction of colchicum in the sixteenth century, Williams' [46] protest "gout: the reproach of medicine" seems appropriate. Modern investigations have in part explained the rationale but have not materially altered the ancient principles of diet in gout. Watson, holding to the allergic theory, has searched for some type of food to which his gouty patients may be hypersensitive. The injudicious use of cinchophen may occasionally be responsible for hepatitis, which may or may not have serious consequences.[47] Watson stated that "iodine in the form of potassium iodide controls the gouty state quite as effectively as cinchophen and much more safely." Summing up the arguments for and against the administration of cinchophen, Hench [49] concluded that if other available analgesics are effective, cinchophen should be avoided,

44. Joslin, E. P.: Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 177.

45. Sears, W. G.: The Occurrence of Gout During the Treatment of Pernicious Anemia, Lancet **1**:24 (Jan. 7) 1933.

46. Williams, Rendell: Gout: The Reproach of Medicine, M. J. & Rec. **135**: 143 (Feb. 3) 1932.

47. Beaver, D. C.: The Pathologic Anatomy of the Liver in Cases of Poisoning by Cinchophen, Proc. Staff Meet., Mayo Clinic **7**:425 (July 20) 1932. Weir, J. F., and Comfort, M. W.: Toxic Cirrhosis Caused by Cinchophen, Arch. Int. Med. **52**:685 (Nov.) 1933.

48. This footnote was deleted by the author.

49. Hench, P. S.: Derivatives of Cinchophen and Their Toxicity, Proc. Staff Meet., Mayo Clinic **7**:427 (July 20) 1932; Derivatives of Cinchophen and Their Toxicity, New England J. Med. **207**:949 (Nov. 24) 1932.

but when other remedies are ineffective, a trial of cinchophen is justified. Statistical data lead one to the conclusion that the chances of fatal poisoning from cinchophen are in reality very slight, the fatality being estimated by the research department of a reputable manufacturing concern as about 1 in 600,000. It has seemed wise to us to follow Weintraub's advice regarding the use of alkalis in association with cinchophen to prevent a possible deposition of urates in acid urine and to discontinue the use of cinchophen if at any time evidences of toxicity present themselves.

PROGRESS IN THE STUDY OF NUTRITION

The past few years have seen a tremendous transition in the field of nutrition. The discovery of the vitamins and of the necessity for certain minerals in food has revolutionized the knowledge of nutrition and has aroused the keen interest not only of the medical profession but also of the public. The new knowledge of vitamins has served as a background for recent trends in nutrition which have been well emphasized by McLester [50] in his statement that "the day was when, in order properly to nourish the sick person, the physician told him what he must not eat; now he is told what he must eat." In other words, the tendency has been to get away from the treatment of disease alone and to consider the general nutritive state of the patient. For many years the interest in nutrition was directed largely to a study of the chemical character, digestion and metabolism of the principal food factors. In more recent times studies of the vitamins and minerals have emphasized in particular the first of these features. As a result there has been a tendency on the part of physicians to forget a very important phase of nutrition, namely, alimentation. In a splendid discussion of problems of nutrition, Mendel [51] has called attention to the lamentable lack of knowledge of alimentation, especially of the mechanism of the absorption of foods.

VITAMINS AND MINERALS

Interest in the vitamins in the past year has been directed particularly toward chemical identification of these essential food factors and their significance in resistance to infection. Because the discovery of the various vitamins came so rapidly and since the amounts essential for health were excessively small, chemical identification was delayed. The average person is likely to think of them as a group of substances perhaps related physiologically, if not chemically. However, added

50. McLester, J. S.: Changing Concepts of Nutrition, J. A. M. A. **103**:383 (Aug. 11) 1934.

51. Mendel, L. B.: The Outlook in the Science of Nutrition, Science **78**:317 (Oct. 13) 1933.

knowledge continually emphasizes the chemical and physiologic differences of these substances. In one respect all known vitamins are similar in that man is dependent on exogenous sources for his supply of them.

Vitamin A.—The relationship of certain natural pigments and vitamin A was early recognized and led subsequently to the demonstration by von Euler in Sweden and by Moore in England that very small doses of the yellow pigment carotene in purified form would cure rats exhibiting symptoms of the lack of vitamin A. Recently evidence has been presented which suggests a relationship between another pigment group, the flavines, and vitamin G. Studies of the chemical relation of carotene and vitamin A and of the nature of the vitamin have progressed to the stage which indicates that while alpha, beta and gamma carotene are sources of vitamin A, beta carotene is the best source. In fact, the recently adopted international standard for vitamin A is pure beta carotene, which has a melting point of 184 C. (336.2 F.) and which is optically inactive. Vitamin A is the primary alcoholic derivative produced by the symmetrical division into two parts of the beta carotene molecule, which has the chemical formula $C_{20}H_{30}O$. There has been great interest in recent years in the study of the occurrence of carotene in various foods and of metabolism and conversion to vitamin A in the animal organism. It has been demonstrated definitely that the carotene and the vitamin A content of various samples of the same type of food may differ considerably. In their studies of fresh fish oils, Lovern, Edisbury and Morton [52] demonstrated that the oils vary in vitamin A content as much as 2,500 times. Halibut liver oil was found to be by far the richest known source of this vitamin, although the vitamin content of various oils of the halibut varied from 0.17 to 10 per cent; not only were there seasonal fluctuations, but in general the older and larger fish proved a better source of supply than the younger and smaller fish. Similarly, a study of the vitamin content of butter by Baumann and Steenbock [53] indicated that butter made in the summer contains a greater concentration of both carotene and vitamin A than that made in other seasons; there is a difference of 100 per cent between the vitamin A content of butter made in April and that of butter made in August. These workers demonstrated also that only 12 per cent of the total vitamin A potency of butter is accounted for by the carotene which is present. The balance is present as vitamin A.

52. Lovern, J. A.; Edisbury, S. R., and Morton, R. A.: Variations in Vitamin A Content of Fish-Liver Oils, with Particular Reference to Seasonal Fluctuations in the Potency of Halibut-Liver Oil, Biochem. J. **27**:1461, 1933.

53. Baumann, C. A., and Steenbock, H.: Fat-Soluble Vitamins: XXXVI. The Carotene and Vitamin A Content of Butter, J. Biol. Chem. **101**:547 (July) 1933.

The intestinal absorption of carotene and vitamin A has been demonstrated to constitute a variable factor in supply. In studies of this phase of metabolism, von Euler and Klussmann [54] demonstrated again the important rôle played by bile salts in absorption, for when dispersed in colloidal form in aqueous fluids carotene does not penetrate biologic membranes, but carotene and carotenoid pigments pass into aqueous solution in the presence of bile salts. It is supposed that following absorption carotene is again displaced from its association with bile salts. From the practical standpoint, Clausen [55] suggested that for rapid storage the feeding of vitamin A is superior to the administration of carotene because the former is more rapidly absorbed and in the presence of fever or diarrhea carotene is poorly absorbed. Similarly, Baumann, Rising and Steenbock [56] found a parallelism in the amount of vitamin A in the diet and that in the liver, even though only from 10 to 20 per cent of ingested vitamin is recovered from this organ. Apparently much of this vitamin is destroyed in the digestive tract.

The liver, recognized for years as the storehouse for vitamin A, is still considered to play an uncertain rôle in its metabolism. The results of earlier studies, which suggested the conversion of carotene to vitamin A by the action of hepatic enzymes have been questioned recently by Drummond and MacWalter,[57] who following the injection of carotene into the portal vein of rabbits found no increase in the amount of vitamin A in the liver for eight days. They were unable to obtain a conversion of carotene to vitamin A in vitro by incubation with liver tissue. Estimations of the vitamin A content of the liver at necropsy have been of interest but have not been illuminating. Muller and Suzman [58] in 106 cases observed at necropsy found a marked variation in the vitamin A content of the liver: in 11.3 per cent of the cases no vitamin A was found, and no relation could be established statistically between the cholesterol and the vitamin A content of the liver.

There is still almost complete ignorance of the facts concerning the mechanism of vitamin A activity. Carotene is almost always present in the blood of persons more than 2 years of age. The amount of carotene or of vitamin A in the blood is not an indication of the amount

54. von Euler, Hans, and Klussmann, Erika: Zur Biochemie der carotinoide und des vitamins C (Ascorbinsäure), Ztschr. f. physiol. Chem. **219**:215, 1933.

55. Clausen, S. W.: Limits of the Anti-Infective Value of Provitamin A (Carotene), J. A. M. A. **101**:1384 (Oct. 28) 1933.

56. Baumann, C. A.; Rising, B. M., and Steenbock, Harry: The Absorption and Storage of Vitamin A by the Rat, J. A. M. A. **103**:114 (July 14) 1934.

57. Drummond, J. C., and MacWalter, R. J.: The Biological Relation Between Carotene and Vitamin A, Biochem. J. **27**:1342, 1933.

58. Muller, G. L., and Suzman, M. M.: The Cholesterol and Vitamin A Content of the Liver in Man: A Study of One Hundred and Six Livers Obtained at Autopsy, Arch. Int. Med. **54**:405 (Sept.) 1934.

which may be stored in the liver. It may be said broadly that the essential function of vitamin A is to maintain the integrity and normal state of the epithelial structure of the animal organism. The close relation of vitamin A to the visual purple of the retina, to the maintenance of a normal epithelial barrier against infection and to growth is evidence of its versatility. As expressed by Orr and Richards,[59] the most important rôle of vitamin A in nutrition lies in its power to prevent the onset of pathologic conditions which are the cause of the loss of weight that occurs in deficiency of vitamin A.

It is almost uniformly understood that states of vitamin A deficiency are rare among civilized peoples. In the past year interesting contributions have been made which suggest that this is not strictly true. For example, Jeans and Zentmire,[60] in a study of sensitivity to light following partial adaptation to darkness of 213 children, found a group (about 20 per cent) with subnormal vision in the dark who were relieved promptly by the use of cod liver oil. They interpreted this as evidence of an abnormality previously unrecognized by the patients and the result of vitamin A deficiency. Further proof must be forthcoming before this important suggestion can be accepted as a fact.

Within the past year sufficient reports have accumulated from reliable sources to establish the occurrence of a distinct dermatologic lesion as the result of vitamin A deficiency. Loewenthal [61] in his study of conditions in East African prisons found that 74 of 81 prisoners had characteristic dermatitis and that 45 had xerophthalmia. Several authors have expressed the opinion that the cutaneous changes occur before either xerophthalmia or night blindness; the latter was previously thought to be the earliest symptom. The cutaneous changes consist of keratinization of a hard, dry, red papular type, resembling goose skin and most marked on the extensor surfaces.[62]

The relationship of vitamin A and infections, which still constitutes a problem requiring further study, will be considered subsequently.

The Vitamin B Complex.—There is ample chemical and physiologic evidence to indicate that the original vitamin B discovered by Funk is in reality a complex and probably consists of several distinct chemical enti-

59. Orr, J. B., and Richards, Marion B.: Growth and Vitamin A Deficiency, Biochem. J. **28**:1259, 1934.

60. Jeans, P. C., and Zentmire, Zelma: A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, J. A. M. A. **102**:892 (March 24) 1934.

61. Loewenthal, L. J. A.: A New Cutaneous Manifestation in the Syndrome of Vitamin A Deficiency, Arch. Dermat. & Syph. **28**:700 (Nov.) 1933.

62. Goodwin, G. P.: A Cutaneous Manifestation of Vitamin A Deficiency, Brit. M. J. **2**:113 (July 21) 1934.

ties. Already, the existence of vitamins B_1, B_2, B_3, B_4 and B_5 have been described, although they are not universally accepted. Vitamin B_2 is recognized by many as vitamin G. Studies of vitamin B_1 in the past year have been limited largely to experimental work. Clinical interest in this vitamin has not been as great as that in other vitamins because the outstanding clinical manifestation of its deficiency, beriberi, is unusual in this country. However, recent studies by Cobb, Strauss and their associates [63] have suggested the importance of this vitamin in neurologic disturbances. It seems a safe conclusion at present that the clinician need have little concern regarding a sufficiency of vitamin B_1 in the diet of the average American. Although vitamin B_1 is apparently not stored in any quantity in the body, its supply is generally abundant and there is no evidence that maximal quantities are of greater value than a normal supply.

The chemical identity of vitamin B_1 is unknown, although active crystalline products have been produced. It appears from the study of Birch and Harris [64] to have the property of a coenzyme-like substance intervening in the chain of reactions in the oxidation of carbohydrate. Apparently it is particularly active in the chain involving the formation and oxidation of lactic acid. Harris and Birch emphasized that vitamin B_1 is not identical with the coenzyme of Benga and Szent-Györgyi for lactic acid dehydrogenase, although closely related to it. In an attempt to determine the structure of vitamin B_1, Sure [65] found that pure irradiated adenine sulphate was a complete failure as a source of vitamin B_1 for growth. The bradycardia characteristic of beriberi and vitamin B_1 deficiency, previously correlated with the accumulation of lactic acid, is corrected by the administration of vitamin B_1. Another physiologic rôle is suggested by the experimental work of Cowgill and Gilman,[66] who concluded that so far as any diminution of the gastric secretion is concerned in animals lacking the vitamin B complex, this is due to absence of the B_1 component. That vitamin B_2 (G) plays a significant rôle in this relationship is unlikely, but the point is not yet proved.

The Second International Conference on Vitamin Standardization recommended the continuance of the previous standard. In fact, the

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63. Minot, G. R.; Strauss, M. G., and Cobb, Stanley: "Alcoholic" Polyneuritis, Dietary Deficiency as a Factor in Its Production, New England J. Med. **208**:1244 (June 15) 1931.

64. Birch, T. W., and Harris, L. J.: Bradycardia in the Vitamin B_1 Deficient Rat and Its Use in Vitamin B_1 Determinations, Biochem. J. **28**:602, 1934.

65. Sure, Barnett: Irradiated Adenine Sulphate as a Source of Vitamin B for Growth, Biochem. J. **27**:2043, 1933.

66. Cowgill, G. R., and Gilman, Alfred: Physiology of the Vitamins: XXIII. The Effect of Lack of Vitamin B Complex on the Secretion of Gastric Juice in Dogs with Gastric Pouches, Arch. Int. Med. **53**:58 (Jan.) 1934.

conference found the previous vitamin B_1 standard to be the most satisfactory that had been established. The standard, of which there is a supply sufficient for many years, is an adsorbate on acid clay.

There may be a need in the future for the parenteral use of vitamins, although the need will likely always be considerably restricted. The recent efforts of Stuart, Block and Cowgill [67] to prepare an inexpensive and easily prepared solution of vitamin B_1 which would be suitable for parenteral use have been successful.

There has been much debate on the significance, so far as deficiency disease is concerned, of atrophy of the mucous membranes of the tongue. Steenbock and his associates [68] presented evidence which they believed showed that atrophic glossitis in the rat and in man is dependent on a deficiency of vitamin B_1. The clinical evidence of this fact is not completely convincing.

Vitamin B_3.—In the mind of some investigators the so-called vitamin B_3 is nothing more than an abundant supply of vitamin B_1. So far as is known, there is no clinical application of this knowledge.

O'Brien [69] has evidence which he believes justifies the opinion that vitamin B_3 is distinct from vitamin B_1; in fact, some features suggest that it is an amino-acid That the whole of the vitamin B complex does not consist of vitamins B_1 and B_2 (G) was strongly suggested by Booher, Blodgett and Page,[70] who found that a vitamin G concentrate with a vitamin B_1 crystalline product did not constitute the vitamin B complex.

Vitamin C.—Recent studies which have elucidated the chemical nature of vitamin C have added another brilliant chapter to the history of scurvy. To Szent-Györgyi [71] and King [72] and their associates must go the credit for independently establishing the fact that vitamin C is cevitamic acid (introduced as ascorbic acid). The chemical formula of cevitamic acid (first called hexuronic acid) is $C_6H_8O_6$. Its powerful capacity as a reducing agent is well recognized, but the exact mechanism of its physiologic action is still not clear. There is debate as to

67. Stuart, E. H.; Block, R. J., and Cowgill, G. R.: The Antineuritic Vitamin: V. The Preparation of a Vitamin Concentrate Suitable for Parenteral Use, J. Biol. Chem. **105**:463 (June) 1934.

68. Hutter, A. M.; Middleton, W. S., and Steenbock, Harry: Vitamin B Deficiency and the Atrophic Tongue, J. A. M. A. **101**:1305 (Oct. 21) 1933.

69. O'Brien, J. R.: Vitamin B_3, Biochem. J. **28**:926, 1934.

70. Booher, Lela E.; Blodgett, H. M., and Page, J. W.: Investigations of the Growth-Promoting Properties of Vitamin G Concentrates, J. Biol. Chem. **107**:599 (Nov.) 1934.

71. Svirbely, S. L., and Szent-Györgyi, Albert: The Chemical Nature of Vitamin C, Biochem. J. **26**:865, 1932.

72. Waugh, W. A., and King, C. G.: Isolation and Identification of Vitamin C, J. Biol. Chem. **97**:325 (July) 1934.

the relation of cevitamic acid to the endocrine glands, particularly to the suprarenals. The most obvious effects of its absence are on the capillaries and perhaps also on the teeth. The loss of normal features by the intercellular capillary substance leads to hemorrhages which are characteristic of scurvy. Other physiologic functions of cevitamic acid, which have been suggested by Harris and Ray,[73] are the maintenance of the functional activity of certain types of cells (osteoblasts, odontoblasts, cementoblasts), and the prevention of their premature degeneration. There is, however, no appreciable local concentration of cevitamic acid in the teeth and in the bones. Presnell [74] added evidence which indicates that in the experimental animal receiving insufficient quantities of vitamin C, the number of blood platelets decreases and anemia occurs; this suggests that the bleeding in scurvy may be caused not only by changes in the vascular system but by alterations in the blood.

In keeping with the recognition that cevitamic acid is vitamin C, the newly adopted international standard for this substance is l-cevitamic acid, as defined by certain physical constants.

Other significant achievements in the chemistry of vitamin C have been the development of an indirect chemical method for the estimation of cevitamic acid by Harris and Ray and the synthesis of cevitamic acid in the laboratory. The former discovery has permitted studies not only of the cevitamic acid content of foods but also of some of the metabolic features of vitamin C. The quantity of cevitamic acid in the juice of various citrous fruits, particularly in lemon juice, previously was thought to be constant. In fact, the first international unit consisted of a certain quantity of lemon juice. However, Bacharach, Cook and Smith,[75] in their studies of the cevitamic acid content of citrous fruits, found variability even in fruit from the same consignment. Oranges contained a mean value of 51 mg. per hundred cubic centimeters, tangerines, 37 mg., and lemons, 64 mg. The storage of fruit for one month caused a loss of only 6 per cent of the cevitamic acid content of lemon juice.

It was estimated by Harris, Ray and Ward [76] that the minimal daily requirement of cevitamic acid is that contained in 30 cc. of orange

73. Harris, L. J., and Ray, S. N.: Standardization of the Anti-Scorbutic Potency of Ascorbic Acid, Biochem. J. **27**:2016, 1933.

74. Presnell, A. K.: The Relation of Avitaminosis C to Blood, J. Nutrition **8**:69 (July) 1934.

75. Bacharach, A. L.; Cook, Phyllis M., and Smith, E. L.: The Ascorbic Acid Content of Certain Citrous Fruits and Some Manufactured Citrous Products, Biochem. J. **28**:1038, 1934.

76. Harris, L. J.; Ray, S. N., and Ward, Alfred: The Excretion of Vitamin C in Human Urine and Its Dependence on the Dietary Intake, Biochem. J. **27**: 2011, 1933.

juice, or about 20 mg. It has been recognized for years that vitamin C is not stored in the body in any great quantity. However, as was demonstrated by Szent-Györgyi,[77] the suprarenal glands contain appreciable quantities of vitamin C. Harris and Ray [78] examined the suprarenal glands of the ox and found that the cevitamic acid content of the medulla is two-thirds that of the cortex and that both are rich in cevitamic acid. In fact, both contain more than orange juice contains, weight for weight. There has been much discussion of the relationship of cevitamic acid and the suprarenal hormone. Grollman and Firor [79] studied the problem and produced evidence which suggests that the apparent intimate relation betwen the suprarenal cortex and the deficiency of vitamins is explainable on the assumption that the hormones and vitamins are necessary for the proper functioning of a great number of organs and tissues. They expressed the belief that the apparent partial replaceability of vitamin C by preparations of the suprarenal cortex is the result of the presence of cevitamic acid in such extracts. On the other hand, cevitamic acid does not prolong the life of suprarenalectomized animals.

In experimental scurvy in guinea-pigs Siehrs and Miller [80] have found that cevitamic acid in the cortex of the suprarenal glands disappears progressively during the progress of the disease. In fact, the staining reaction to silver nitrate indicates a decrease in the cevitamic acid content after the animal has been on a scorbutic diet for one day, and a minimum amount of staining occurs on the sixth day. When 3 cc. of orange juice is fed there is a prompt reappearance of acid in the cortex of the suprarenal glands.

Under ordinary conditions cevitamic acid is excreted in the urine in approximately uniform quantities. This amounts to about 30 mg. daily, according to Harris, Ray and Ward. The importance of this observation cannot yet be estimated. It is possible that a measurement of the amount of cevitamic acid in the urine will prove of value clinically. In studies of the effect of the ingestion of large quantities of cevitamic acid on urinary excretion, Harris, Ray and Ward demonstrated that if 600 cc. of orange juice was given, the concentration of cevitamic acid in the urine rose sharply to from eight to ten times the normal

77. Szent-Györgyi, Albert: Observations on the Function of Peroxidase Systems and the Chemistry of the Adrenal Cortex, Biochem. J. **22**:1387, 1928.

78. Harris, L. J., and Ray, S. N.: Vitamin C in the Suprarenal Medulla, Biochem. J. **27**:2006, 1933.

79. Grollman, Arthur, and Firor, W. M.: Studies of the Adrenal: VII. The Relation of the Adrenal Cortical Hormone to the Vitamins, J. Nutrition **8**:569 (Nov. 10) 1934.

80. Siehrs, A. E., and Miller, C. O.: Disappearance of Vitamin C from the Adrenals of Scorbutic Guinea Pigs, J. Nutrition **8**:221 (Aug. 10) 1934.

amount and then rapidly dropped to normal within one day. The normal daily loss of from 30 to 33 mg. is maintained even though the subject remains on a diet free from vitamin C for one week. This amount, incidentally, is greater than the daily requirement of cevitamic acid for man; however, the average person consumes more than his actual requirement. Johnson and Zilva [81] suggested some variability in the urinary excretion of cevitamic acid, depending on the amount stored in the body and on the quantity consumed in the food. They discovered that with a complete store in the body a more or less constant level of excretion is maintained.

Parenteral injections of preparations of vitamin C have been used for several years. Dry [82] mentioned the intravenous use of buffered orange juice in cases of scurvy. Bauke,[83] by giving 100 mg. of l-cevitamic acid intravenously each day to a patient who had scurvy, recently obtained good results and an apparent reduction in the period of recovery.

There has been much discussion of the value of tests of capillary resistance in the diagnosis of latent scurvy. Schultzer [84] and Dalldorf,[85] who have faith in such tests, found latent scurvy to be not uncommon among hospital patients and children from poor homes. However, others have insisted that decreased capillary resistance is not sufficient evidence of deficiency of vitamin C. It seems reasonable to place the burden of proof on those who accept the test. It is difficult to believe that latent scurvy is as common as some of the studies indicate.

The relation of vitamin C to dental caries is still a subject of such wide debate and uncertainty that it will not be considered at this time.

Vitamin D.—Recent interest in vitamin D has been concerned chiefly with (1) the daily requirement of adults and children, (2) the most satisfactory form in which it may be administered and (3) its significance in rickets and dental caries.

It is widely accepted that vitamin D is viosterol (irradiated ergosterol), probably one of the many possible stereo-isomers of ergosterol. There is still evidence which tends to prevent the universal acceptance

81. Johnson, S. W., and Zilva, S. S.: The Urinary Secretion of the Ascorbic and Dehydroascorbic Acids in Man, Biochem. J. **28**:1393, 1934.

82. Dry, T. J.: Avitaminosis in Natives of Rhodesia, Arch. Int. Med. **51**: 679 (May) 1933.

83. Bauke, E. E.: Parenterale C—Vitamin—(Cebion—) Behandlung bei Skorbut, München. med. Wchnschr. **81**:1240 (Aug. 10) 1934; abstr., J. A. M. A. **103**:1187 (Oct. 13) 1934.

84. Schultzer, P.: Studies on Capillary Resistance: I. Lowered Resistance Due to Vitamin C Deficiency and Other Conditions in Hospitalized Patients, Acta med. Scandinav. **81**:113, 1934.

85. Dalldorf, G.: Sensitive Test for Subclinical Scurvy in Man, Am. J. Dis. Child. **46**:794 (Oct.) 1933.

of viosterol as the only antirachitic factor despite its preparation in crystalline form. Kon and Booth [86] suggested, for example, a true chemical difference between the antirachitic factor of butter and the antirachitic factors of cod liver oil and viosterol.

The international unit for vitamin D has remained unchanged, consisting of viosterol in olive oil.

One difficulty which has arisen in experimental work on vitamin D is that animals do not utilize different antirachitic materials in the same proportion. This variation in the utilization of antirachitic material by the same or different organisms is still unexplained. Friedman,[87] after an extensive review of the literature, pointed out, for example, that there is extensive clinical evidence to the effect that far fewer units of vitamin D in the form of milk containing vitamin D are required to protect against, or to heal, rickets than are required with other antirachitic agents. His studies suggest that of the various methods of augmenting the vitamin D content of milk, the most satisfactory are the direct irradiation of the milk and the direct addition of vitamin D concentrates to milk.

Despite the fact that information is now at hand which should permit the prevention and healing of rickets, the disease is still prevalent. Harris [88] noted that recent official reports disclose that no less than from 80 to 90 per cent of the elementary school population in London shows evidence of some degree of rickets. There is discussion as to the most satisfactory method of preventing and of healing rickets and as to the relationship of the optimal and toxic doses of the various antirachitic agents. Irradiated yeast, viosterol, cod liver oil and milk which has been augmented with vitamin D are advocated. The very important question of the advisability or practicability of augmenting all milk with vitamin D has been raised. The answers to all of these questions are not ready. Further experimental work and clinical observation will be necessary before it can be stated definitely what is the optimal requirement for each of the various antirachitic preparations.

The mechanism of action of vitamin D in the normal mineralization of bone and in the prevention and healing of rickets is not clear. The suggestion is made that vitamin D not only increases the absorption of calcium and of phosphorus but acts in other phases of the metabolism of bone.

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86. Kon, S. K., and Booth, R. G.: The Vitamin D Activity of Butter: I. A Chemical Differentiation of the Antirachitic Factor of Autumn and Winter Butter from Irradiated Ergosterol and Vitamin D of Cod Liver Oil, Biochem. J. **27**: 1302, 1933.

87. Friedman, Samuel: Vitamin D Milk: A Résumé, J. Pediat. **4**:678 (May) 1934.

88. Harris, L. J.: The Significance of Vitamins in Practical Experience, Brit. M. J. **2**:367 (Aug. 26) 1933.

Another interesting aspect of the metabolism of vitamin D is suggested by the studies of Light, Wilson and Frey,[89] who found that when vitamin D is supplied as irradiated yeast in the diet of the cow it is practically completely absorbed, that it disappears rapidly from the blood at a maximal rate of 10 per cent per hour and nevertheless that only from 2 to 3 per cent appears in the milk. The place and manner of destruction of the remainder are unknown. A slight amount of it is reexcreted into the intestine.

The significance of vitamin D in dental caries is such a disputed problem that it will not be considered here.

Vitamin G (B_2).—Recent interest in vitamin G has centered about its significance as a hematopoietic substance and about its relation to pellagra. The brilliant work of Castle,[90] which has been confirmed by others, at first suggested that vitamin G might be the extrinsic factor which when combined with an intrinsic factor supplied normally by the gastric mucosa forms an active and normal hematopoietic agent. The evidence of this relationship is not well established, and the recent work of Wills [91] and of the Lassens [92] suggests that the extrinsic factor is not vitamin G, because normal gastric juice incubated with purified sources of vitamin G was discovered to be ineffective in producing a remission when fed to patients who had pernicious anemia.

Conservative clinicians have remained somewhat skeptical about accepting the evidence that a deficiency of vitamin G is entirely responsible for pellagra, despite the splendid early work of Goldberger and his associates. In the past year further evidence of an unknown factor in the production of pellagra has been advanced. McLester [93] called attention to the apparent impossibility of invariably relating pellagra to faulty diet, to the failure in many cases to correct this disorder by dietary means and to the epidemiologic characteristics of the disease. He expressed the belief that the most likely etiologic factors, in the order of prominence, are multiple food deficiency and, directly or indirectly, infective agents. It seems reasonable to agree with McLester that, despite the careful work that has been done, the last word regarding the nature of pellagra is yet to be said.

89. Light, R. F.; Wilson, L. T., and Frey, C. N.: Vitamin D in the Blood and Milk of Cows Fed Irradiated Yeast, J. Nutrition **8**:105 (July) 1934.

90. Castle, W. B., and Locke, E. A.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, J. Clin. Investigation **6**:2 (Aug.) 1928.

91. Wills, Lucy: The Nature of the Haemopoietic Factor in Marmite, Lancet **1**:1283 (June 17) 1933.

92. Lassen, C. A., and Lassen, H. K.: Yeast or Vitamin B_2 as "Extrinsic Factor" in Treatment of Pernicious Anemia, Am. J. M. Sc. **188**:461 (Oct.) 1934.

93. McLester, J. S.: The Nature of Pellagra: A Critique, Ann. Int. Med. **8**: 475 (Oct.) 1934.

The chemical nature of vitamin G is not certain. A relationship to the pigment group of the flavines is apparent. At the Second International Conference on Vitamin Standardization the establishment of pure lactoflavine as a standard for vitamin B_2 (G) was considered, but its use was held to be premature. One reason for this attitude was that a deficiency of vitamin G is not definitely connected with any disease or syndrome which affects man. This is a rather remarkable conclusion when one takes into consideration that, in America at least, it is widely recognized and accepted by many that a deficiency of vitamin G leads to the development of pellagra. However, the conclusion of the conference, which was formed by a distinguished group of scientists, was unanimous.

If the results in animals obtained by Sherman and Ellis [94] with vitamin G can be confirmed in man, one of the most interesting and important developments in the knowledge of nutrition lies ahead. These investigators have been feeding rats with amounts of vitamin G at four different levels. The young of rats with the highest intake of vitamin G showed a superior vitality and a prolongation of the period between the attainment of maturity and the onset of senility. These experiments reaffirm previous work by Sherman and make clear that the optimal intake of vitamin G is much more than the amount demonstrated as strictly necessary. It seems reasonable to speculate that this may be true also of some of the other essential food factors.

Vitamin E.—While vitamin E is recognized as being essential for certain experimental animals, there is still no evidence that it has any clinical significance in man.

Excessive Dosage of Vitamins and of Foods Containing Them.—While the qualitative aspects of vitamins as essential food factors are well recognized, there is a paucity of information with regard to the quantitative requirements. This has led to much confusion, which has been increased by the lack of information concerning the chemistry, absorption and metabolism of the vitamins. Consequently it has been impossible to establish levels of minimal requirement, and there has been speculation as to the optimal requirement and as to whether larger than optimal quantities of a vitamin will lead to improvement in health and greater resistance to infection. It has been suggested that this is true in the case of vitamins A and G. With the preparation of vitamins in concentrated and crystalline form and because the vitamins normally seem to be required only in minute amounts, the problem has arisen of the possibility of toxic effects from excessive doses. On this point there are several interesting observations.

94. Sherman, H. C., and Ellis, L. N.: Necessary Versus Optimal Intake of Vitamin G (B_2), J. Biol. Chem. **104**:91 (Jan.) 1934.

Considerable interest has been aroused in the toxicity of excessive doses of cod liver oil. It is true, as Cox and Roos [95] pointed out, that the toxicity of cod liver oil must be considered separately from hypervitaminosis D, since the dosage of cod liver oil necessary to induce pathologic calcification would have to be calculated in liters. Andersson,[96] experimenting with white mice and using daily doses of 3 cc. of cod liver oil per kilogram of body weight, found pathologic changes characterized by pigmentary and vacuole degeneration of muscle, transformation of the muscle cells into connective tissue and sometimes fatty infiltration and calcareous and waxy degeneration of the muscles. Apparently complete restitution to normal never occurred after the cessation of the administration of cod liver oil. Cox and Roos could demonstrate no histologic lesions in the hearts of rats which for one hundred and thirty days had been fed a diet which was adequate in protein, salts and vitamins and contained 78 per cent of calories as cod liver oil, but the rate of growth was definitely subnormal. The amount of cod liver oil administered in these experiments was 27.3 Gm. for each kilogram of body weight. In an attempt to explain abnormal changes after the administration of cod liver oil, such as those reported by Agduhr, Cox and Roos suggested that the toxic effects noted by others after the use of doses one-sixtieth as large as theirs may have been the result of a faulty interpretation of the histologic sections, of a deficiency of some accessory food constituents or of the presence of toxic substances in the oil.

The toxic effect of excessive quantities of viosterol possibly may be explained by the presence of toxic products. This may explain such toxic manifestations as have followed the administration of relatively low doses of viosterol, although Drummond [97] stated that it has been finally proved that the toxicity may be the result of exaggerated action of the vitamin as well as the result of toxic contaminants. Hauch [98] noted that, in general, the more complete and better balanced a diet is, the more protection it gives against the toxicity of excessive amounts of vitamin D.

In a discussion of the symptoms of overdosage of viosterol in his studies of 300 subjects, Reed [99] pointed out that toxicity in many cases

95. Cox, W. M., and Roos, A. J.: On the Alleged Toxicity of Cod Liver Oil, Bull. Johns Hopkins Hosp. **44**:430 (June) 1934.

96. Andersson, Hjalmar: Concerning Some Cod Liver Oil Lesions and Their Healing Tendency, Upsala läkareförh. **39**:27 (Dec.) 1933; abstr., J. A. M. A. **102**:810 (March 10) 1934.

97. Drummond, J. C.: Biochemical Studies of Nutritional Problems, Lane Medical Lectures, Stanford University, Calif., Stanford University Press, 1934.

98. Hauch, J. T.: Studies on the Effect of High Doses of Irradiated and Non-Irradiated Ergosterol on the Albino Rat, J. Nutrition **8**:163 (Aug. 10) 1934.

99. Reed, C. T.: Symptoms of Viosterol Overdosage in Human Subjects, J. A. M. A. **102**:1745 (May 26) 1934.

may be recognized very early by the subjects themselves and before any serious damage has occurred. An increased frequency of urination is the most common initial symptom. Anorexia and nausea also occur; acute gastro-intestinal symptoms appear later, but there is no fever. Muscular weakness, lassitude, dull aching in the muscles, dizziness and disturbed muscular coordination and equilibrium may develop. It appears from these studies that there need be no apprehension about the administration of amounts ranging up to 150,000 international units daily for an indefinite period (the normal antirachitic dose is 3,000 international units). In contrast to this, Harris stated that the minimal toxic dose is 10,000 international units daily. This investigator, who has expressed the belief that viosterol is the best antirachitic agent in the treatment of rickets, has suggested that the toxic dose is close to the optimal daily therapeutic dose of from 3,000 to 5,000 units.

In their studies of the effect of large doses of vitamin A, Davis and Moore [100] reported that with large, nontoxic doses the amount in the liver was very high. The lungs and kidneys also held some vitamin A, but other organs contained very little, with the exception of the suprarenal glands. With massive doses of vitamin A in young rats there developed emaciation, hemorrhagic retinitis and a loss of hair about the mouth. Hypervitaminosis A could not be produced by feeding carotene because carotene is of limited solubility and therefore of limited dosage.

Toxic manifestations from excessive quantities of vitamin A have not been reported in man. Similarly, the effect of excessive doses of vitamin B is unknown. Demole [101] could find no evidence experimentally of hypervitaminosis C. In dogs receiving l-cevitamic acid in large doses there developed no symptoms or histologic changes. Excessive quantities of cevitamic acid are rapidly excreted in the urine.

In summarizing the evidence it seems fair to state that with the exception of the established toxicity of very large doses of viosterol or of smaller doses of improperly irradiated ergosterol there need be little concern at present on the score of overdosage of the vitamins.

Iron and Copper.—There has been much clinical interest in recent years in the relationship of iron and copper to the formation of hemoglobin. The work of Whipple in studying the effect of various foods on the regeneration of hemoglobin in dogs in which the hemoglobin reserves had been depleted by repeated bleeding served as the initial

100. Davis, A. W., and Moore, Thomas: Vitamin A and Carotene: XI. The Distribution of Vitamin A in the Organs of the Normal and Hypervitaminotic Rat, Biochem. J. **28**:288, 1934.

101. Demole, Victor: On the Physiological Action of Ascorbic Acid and Some Related Compounds, Biochem. J. **28**:770, 1934.

stimulus. Additional stimulus has been afforded by Mackay's recognition of the frequency of anemia in infancy and by the proof offered by her that the principal factor in the production of this anemia is a dietary deficiency. Much useful information will be found in the splendid review of Davidson and Leitch [102] of the nutritional anemia which affects man and animals. Some of the significant points are the following: A deficiency in the diet of any element essential for the formation of erythrocytes, namely, constituents of the organic matrix or stroma, pyrrol either as protoporphyrine or in some simpler form, iron and the constituent amino-acids of globin, can lead to the development of anemia. Extensive studies reveal a wide range of the iron content of milk. Not only may there be a variation in the iron content of various foods, but it must be recalled that although an adequate quantity is present in food, this does not necessarily indicate a high content of iron in a form which is capable of absorption. The old idea of Bunge that only organic iron is absorbed has been replaced through demonstrations that iron to be absorbed must be soluble, ionizable and ultrafiltrable. The iron of food is apparently wholly or chiefly ferric iron, and its availability depends largely on the presence of acid in the stomach, which plays a rôle in the production of ferrous iron, the form in which iron is apparently absorbed. Davidson and Leitch pointed out that in achlorhydria there may be difficulty in liberating iron in food from the complexes in which it occurs and in reducing it to ferrous iron.

Studies of the requirements and storage of iron give variable results. While Sherman has suggested a standard of 15 mg. per day, Davidson and his associates have demonstrated that health may be maintained in children and in adult men, but not always in women, on as little as 6 mg. per day. While evidence indicates that the amount of iron in the liver is easily increased by feeding iron and that it is regulated also by the rate of the destruction of erythrocytes, the amount of iron in the spleen and kidneys appears to depend chiefly on the latter factor. An important factor, not itself a constituent of the hemoglobin molecule, affecting the utilization of iron and the formation of hemoglobin is copper. Copper is contained in particular in liver, oysters, chocolate, cocoa and molasses.

From the standpoint of considering anemia as a disease of nutritional deficiency it is necessary to describe one group as "direct," or the result of an actual quantitative insufficiency of the factors necessary for the formation of blood, and another group as "indirect," or the result of a failure of absorption from the intestinal tract. In the prevention and treatment of nutritional anemia of adolescence, Davidson and Leitch suggested a daily supply of from 15 to 20 mg. of iron, a quantity easily

102. Davidson, L. S. P., and Leitch, I.: The Nutritional Anaemias of Man and Animals, Nutrition Abstr. & Rev. **3**:901 (April) 1934.

obtained if reasonable care is paid to the ingestion of foods rich in iron. Women, who commonly have anemia, present a more difficult problem because of the simultaneous occurrence, frequently, of other etiologic factors. Iron and ammonium citrate in a dose of 30 grains (1.95 Gm.) three times a day, pills of ferrous carbonate, U. S. P., in a dose of 15 grains (0.97 Gm.) three times a day, reduced iron in a dose of 10 grains (0.64 Gm.) three times a day and ferrous sulphate, ferrous carbonate or ferrous chloride in a dose of 3 grains (0.19 Gm.), three times a day are equally efficacious in treatment. Evidence is steadily accumulating to show that the efficacy of a preparation of iron depends largely on the number of ferrous ions which are liberated in the small intestine. The advantages of adding copper in the treatment of nutritional anemia remain questionable. The amount of copper required is very small and is supplied by the copper which exists as an impurity in the preparations of iron dispensed for therapeutic purposes.

More information with regard to the requirement of iron and copper of growing children has been obtained from studies of the retention of iron and copper by Daniels and Wright.[103] They found the intake of iron of eight normal children from 4 to 6 years of age to range from 0.57 to 0.75 mg. for each kilogram of body weight, from 94 to 97 per cent of the excreted iron appearing in the feces. The daily intake of copper amounted to from 0.069 to 0.113 mg. for each kilogram of body weight. The excreted copper appeared largely in the feces. Undernourished children retained larger quantities of these essential elements than did children who were well nourished. The larger retention of copper, in general, occurred when the diet contained a larger quantity of this element. However, the amount of copper retained bore no constant relationship to the amount of iron retained.

RELATION OF THE NUTRITIVE STATE TO INFECTION

It is logical to suppose that there is a close relationship between the state of nutrition and the resistance to infection. It would be anticipated that the undernourished person would be more susceptible to the development of an infectious disease than the well nourished person. When one looks for evidence to substantiate this impression the search is not too fruitful. Interest in this subject was precipitated by the observation that animals which had been deprived of vitamin A were subject to infections, particularly of the eye. The public now is being bombarded with advertising of the "anti-infective" power of foods or drugs containing this or that vitamin, such as is found in the cough drops of the well known brothers "Trade" and "Mark."

103. Daniels, Amy L., and Wright, Olive E.: Iron and Copper Retentions in Young Children, J. Nutrition **8**:125 (Aug.) 1934.

The most important practical problem is not so much whether a person receiving an inadequate diet is less capable of resisting infection than is a normal person, but whether the amount of vitamin in excess of that normally obtained by well nourished persons will further increase the resistance to infection. In the past year there have appeared two extensive reviews on this subject. While the approach has been somewhat different in each case, the conclusions are much the same. The possibility that the diet may have some influence on the incidence, the course and the final outcome of infection is a comparatively recent idea. Among some of the difficulties raised by such a problem are the inability to subject patients to a controlled nutritional program, the ignorance of quantitative requirements of the vitamins and the lack, until recently, of pure preparations of the vitamins for experimental purposes. Consequently much that has been written on this subject is based on experiments on animals and on observations on relatively small groups of persons. Clausen [104] in his review came to the general conclusion that the susceptibility to infection is not, as a rule, affected by the diet but that resistance to infection, on the other hand, may be greatly diminished by a deficient diet. He said: "A deficiency in the diet of vitamins A and C appears quite definitely to lower resistance to infection. In certain cases, a lack of the vitamin B complex may also do the same thing. A lack of vitamin D cannot be said to have a proven effect in lowering resistance. It seems probable that the existence of a partial deficiency of vitamins may result in loss of resistance to infection, though this cannot be said, from the present evidence, to have been clearly established."

Resistance to infection is accomplished by different protective and immunologic factors and reactions. Consequently, a study of the effect of the vitamin content of the diet on the resistance to infection must take these several factors into consideration. Robertson [105] in her review has considered the available evidence with four criteria in mind: (1) a determination of any change in the natural immune bodies and in the cellular reactions which are the result of deficiency; (2) the assay of responses of the antibodies after the injection of appropriate antigens into experimental animals; (3) the relative liability to spontaneous infection after the defective feeding of animals, and (4) the comparative susceptibility to induced infections of persons who receive inadequate and those who have adequate diets. The conclusion is that although vitamin A is called the anti-infective vitamin little actual evidence exists with regard to this phase of its activity. The opinion

104. Clausen, S. W.: The Influence of Nutrition on Resistance to Infection, Physiol. Rev. **14**:309 (July) 1934.

105. Robertson, E. C.: The Vitamins and Resistance to Infection, Medicine **13**:123 (May) 1934.

is expressed that beneficial effects follow its administration only when a patient has been subsisting on a diet that is partially deficient in vitamin A. Immunologic evidence is presented to show that neither scurvy nor a deficiency in vitamin B is attended by a consistent variation in the resistance to infection. On the whole, the effects of vitamin D in infection, which have been noted by many workers, have been variable, and it is impossible to draw satisfactory conclusions at present.

Several studies which have been reported since the reviews of Clausen and Robertson deserve attention. Beard,[106] for example, studied a group of 36 medical students, to each of whom were administered nine tablets daily for one year of a proprietary preparation of cod liver oil concentrate which contained vitamins A and D. In this group there was a reduction of 50 per cent in the incidence of colds, and 68 per cent of the infections which occurred were mild. On the other hand, there was no difference between the controls and those who took the concentrates so far as the incidence of influenza during an epidemic was concerned. Similarly, the Gardners[107] thought that supplementing the diet of school children with halibut liver oil or with foods particularly rich in vitamin A decreased the incidence of colds and produced a higher degree of general health, as shown by a greater gain in weight. Mackay[108] compared young children in London who received supplementary vitamin A with children who depended on dried milk until 8 months of age and thereafter on dried milk and ordinary table food for their supply of vitamin A. The incidence of minor "infective" lesions of the skin (sore buttocks, intertrigo and so forth) in the children who received added vitamin A was apparently only half that in the control group. There was no difference between the groups in growth, in the rate of gain in weight, in the incidence of respiratory or digestive diseases or in the number of infections. The significance of these findings is debatable, as Mackay pointed out, and may be representative of the fact that vitamin A deficiency is a common occurrence in infants who are artificially fed.

It is obvious from the conflicting character of the data that much more information is needed before the question at issue can be answered. The present position is well stated in an editorial[109] in *The Journal of*

106. Beard, H. H.: The Prophylactic Effect of Vitamin A and D upon the Prevention of the Common Cold and Influenza, J. Am. Diet. A. **10**:193 (Sept.) 1934.

107. Gardner, Esther L., and Gardner, F. W.: Vitamin A and Colds, Am. J. Dis. Child. **47**:1261 (June) 1934.

108. Mackay, Helen M. M.: Vitamin A Deficiency in Children: II. Vitamin A Requirements of Babies; Skin Lesions and Vitamin A Deficiency, Arch. Dis. Childhood **9**:133 (June) 1934.

109. Nutrition and Resistance to Infection, editorial, J. A. M. A. **103**:994 (Sept. 29) 1934.

the American Medical Association: "Despite the many demonstrated correlations between lack of an essential dietary factor and functional and structural change in the organism, there is surprisingly little cogent evidence of a specific relation between these factors and infection."

SIGNIFICANCE OF THE GASTRO-INTESTINAL TRACT IN NUTRITIONAL STATES

Bacteriologic and chemical studies created an erroneous conception of the nature of many diseases, since they gave rise to the thought that disease is always the result of the presence of some abnormal factor or positive agent in the living organism. This thesis became so firmly established that the opposite conception, namely, that the absence of a factor necessary for normal health can produce disease, was overlooked until the vitamins were discovered. And until recently too much emphasis probably was placed on the conception that diseases of dietary deficiency arise solely from a lack in the diet of a sufficient quantity of certain essential food factors. This undoubtedly is the most common cause of clinical and experimental states of deficiency, but it must be emphasized that deficiency may also result from a failure of adequate absorption or utilization of essential food factors. This last conception, which Strauss [110] said originated with Fenwick in 1880, has been developed only in the past few years. It seems reasonable to believe that in this country a large proportion of deficiency states arise from this cause, because the diet of the average American is probably adequate in its qualitative and quantitative aspects. The conception of the rôle of the gastro-intestinal tract in deficiency diseases, in brief, is that a deficiency disease in man may and frequently does develop in spite of an apparently adequate diet because of some disturbance of the gastro-intestinal tract. Attention has already been called to the lamentable lack of information with regard to alimentation. As Mendel has emphasized, there is a paucity of new or novel information about alimentation as well as a need of additional facts secured through new methods of attack on the problem of alimentation and absorption.

Among diseases which have been classified as belonging to the group which result from disturbances in gastro-intestinal function are: pernicious anemia; pellagra; the polyneuritis of alcoholism and that of pregnancy; idiopathic hypochromic anemia, and the toxemia associated with intestinal obstruction and vomiting of pregnancy. Similarly, instances of night blindness, beriberi, pellagra, and nutritional edema have been described as a result of gastro-intestinal lesions which pre-

110. Strauss, M. B.: The Rôle of the Gastro-Intestinal Tract in Conditioning Deficiency Disease: The Significance of Digestion and Absorption in Pernicious Anemia, Pellagra and "Alcoholic" and Other Forms of Polyneuritis, J. A. M. A. **103**:1 (July 7) 1934.

vent an adequate absorption of the essential food factors. Changes in the gastro-intestinal tract which may lead to the development of such conditions include: atrophy of the mucous membrane; changes in the secretion of normal digestive juices or other substances; the absence of the bile salts; the loss of normal gastro-intestinal secretion, as in diarrhea and vomiting, and, last, mechanical factors which obstruct or prevent the contact of foods with a sufficient area of intestinal mucosa to permit adequate absorption.

The studies of Castle indicate that pernicious anemia is a deficiency disease in which the deficiency is the result, not of a defective diet, but usually of the absence from the gastric juices of a specific factor, which is not hydrochloric acid, pepsin, rennin or lipase. A number of cases have been described of a condition identical with pernicious anemia, in which there are various organic abnormalities of the digestive tract and in which occasionally the examination of the gastric juice reveals the presence of the so-called intrinsic factor of Castle.

Thus it seems to have been demonstrated that pernicious anemia may be the result of a lack of a digestive juice in the stomach, the absence from the diet of a substance previously thought to be closely related to vitamin G or the failure of absorption from the intestine of the product of interaction of the gastric juice and the extrinsic factor.

There are in the literature numerous reports of cases of deficiency states which apparently are the result of failure of adequate alimentation in the face of an apparently normal diet. This has been well established in the case of pellagra, which is observed to affect particularly patients who have carcinoma of the stomach and associated pyloric obstruction (Eusterman and O'Leary [111] and others). Night blindness attributable to a deficiency of vitamin A, which apparently is the result of inadequate absorption of the vitamins in the presence of a gastrocolic fistula which side-tracked the small intestine, has been reported by Wilbur and Eusterman.[112] An instance of beriberi following entero-enterostomy in which all but 24 inches (60.9 cm.) of the small intestine was side-tracked has been recorded by Urmy and his associates.[113] Definite relief occurred after the administration of yeast, but complete relief was not obtained until the long blind loop of small intestine was restored to normal continuity.

111. Eusterman, G. B., and O'Leary, P. A.: Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastro-Intestinal Tract: Report of Thirteen Cases, Arch. Int. Med. **47**:633 (April) 1931.

112. Wilbur, D. L., and Eusterman, G. B.: Nutritional Night Blindness: Report of a Case, J. A. M. A. **102**:364 (Feb. 3) 1934.

113. Urmy, T. V.; Ragle, B. H.; Allen, A. W., and Jones, C. M.: Beriberi Secondary to Short-Circuited Small Intestine, New England J. Med. **210**:251 (Feb. 1) 1934.

Strauss and his associates have presented evidence which indicates that multiple neuritis of the "alcoholic" type and that of pregnancy are actually deficiency states. Other diseases which are reported to be the result of inadequate intestinal absorption are: osteomalacia and tetany in celiac disease and sprue; "achlorhydric anemia," which is caused by a deficiency of iron; the so-called "toxic state," which is associated with intestinal obstruction and pregnancy and which is the result of a loss of water and electrolytes, and nutritional edema, which is the result of inadequate absorption in intestinal tuberculosis.

Although factors of intestinal absorption are undoubtedly exceedingly important, as has been stressed, attention should be called to the fact that deficiency states may develop in patients who have gastrointestinal disease and who as a result of symptoms or of poor advice partake of an inadequate diet. The occasional development of scurvy in patients who are receiving treatment for peptic ulcer is a good demonstration of this fact.

There has been much interest in the effect of liquid petrolatum on the absorption of vitamin A and carotene because this substance is so widely used therapeutically. Earlier studies indicated that it has little influence on the absorption of these substances, but recently Dutcher and his collaborators [114] investigated the problem and came to the conclusion that the vitamin A potency of butter fat is lowered when butter fat is fed in small amounts in the presence of liquid petrolatum. With a larger amount of butter fat and a small amount of liquid petrolatum the deleterious effect of the latter is less marked, although still noted. The vitamin A potency of cod liver oil and its concentrates, on the other hand, is not adversely affected by liquid petrolatum. The explanation of this apparent discrepancy is that the carotene of butter is excreted in the unabsorbed liquid petrolatum, supposedly because of the greater solubility in the hydrocarbons of liquid petrolatum than in the lipids of the intestinal juices. The opposite is true of the solubility of vitamin A.

The absorption of iron from the intestinal tract cannot fail to be of interest to the clinician. The work of Heubner and Lintzel, as reviewed by Davidson and Leitch,[102] indicates that ferric iron is unlikely to remain for any length of time in a free state in the digestive tract, even in the absence of food, because it combines with mucus. However, during digestion the combined effects of a low oxygen tension, an abundance of readily oxidizable organic substances and an acid reaction provide conditions in which the conversion of ferric iron to ferrous iron is more likely to occur than is the reverse. It is probable,

114. Dutcher, R. A.; Harris, P. L.; Hartzler, Eva R., and Guerrant, N. V.: Vitamin Studies: XIX. The Assimilation of Carotene and Vitamin A in the Presence of Mineral Oil, J. Nutrition **8**:269 (Sept.) 1934.

therefore, that part at least of the soluble iron is reduced to ferrous iron, that only this part remains ionizable and absorbable and that absorption takes place as ferrous iron. Davidson and Leitch further pointed out that since the iron of food is wholly or chiefly ferric iron and because the availability of iron depends largely on the presence of acid in the stomach for its reduction to ferrous iron, there may be difficulty in liberating the iron of the food and in reducing it to ferrous iron in cases of achlorhydria. This in part may account for so-called "achlorhydric anemia" (hypochromic anemia) and suggests the importance of the administration of ferrous salts in its treatment.

News and Comment

ELLA SACHS PLOTZ FOUNDATION FOR THE ADVANCEMENT OF SCIENTIFIC INVESTIGATION

The original purposes for which the Ella Sachs Plotz Fund was to be used were: (1) researches directed toward the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery; (2) researches preferably on a single problem or on closely allied problems, it being hoped that investigators in this and other countries may be found whose work on similar or related problems may be assisted so that more rapid progress may be made possible; (3) for the purchase of apparatus and supplies that are needed for special investigations and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus or materials which are ordinarily a part of laboratory equipment. Stipends for the support of investigators will be granted only under exceptional circumstances.

In the past year the policy outlined in section 2 has been neglected. During the present great need for funds, grants will be given in the sciences closely related to medicine, without reference to special fields. The maximum size of the grants will usually be less than $500.

During the eleventh year of the foundation eighty-three applications for grants were received by the trustees, forty of which came from the United States, and the other forty-three from thirteen countries in Europe, Asia and Africa. The total number of grants made during this year was twenty-seven, one of these being a continued annual grant. Fourteen of the new grants were made to scientists outside the United States.

In the eleven years of its existence the foundation has made two hundred and twenty-seven grants, and investigators have been aided in Argentina, Austria, Belgium, Chile, China, Czechoslovakia, Estonia, France, Germany, Great Britain, Hungary, Italy, Jugoslavia, Latvia, The Netherlands, Palestine, Poland, Portugal, Roumania, South Africa, Sweden, Switzerland, Syria and the United States.

Applications for grants for the year 1935-1936 should be sent to Dr. Joseph C. Aub, Collis P. Huntington Memorial Hospital, 695 Huntington Avenue, Boston, and must be in the hands of the executive committee before May 1, 1935. Letters asking for aid must state definitely the qualifications of the investigator, the character of the proposed research, the size of grant requested and the specific use of the money to be expended. Letters of recommendation from the directors of laboratories or clinics in which the work is to be done should be included.

LEA AND FEBIGER PUBLISH MEMORIAL VOLUME

In recognition of one hundred and fifty years of publishing, Lea & Febiger have just made available a sketch originally prepared by Henry Charles Lea in 1885 to celebrate the one hundredth anniversary of the founding of their business, revised and amplified to bring it up to date. The volume is beautifully illustrated with facsimiles of letters and fine portraits. This company has been operated continuously by members of the same family. The first editor of the *Philadelphia Journal of the Medical and Physical Sciences*, established in 1820, later the *American Journal of the Medical Sciences*, was Nathaniel Chapman, who was also the first president of the American Medical Association. The publication became the *American Journal of the Medical Sciences* in 1827, under the editorship of Dr. Isaac Hays, who was also in charge of the committee that prepared the Principles of Ethics of the American Medical Association. The company takes particular pride in its continuous publication in America of Gray's "Anatomy," beginning in 1859.

SEVENTH INTERNATIONAL CONGRESS ON INDUSTRIAL ACCIDENTS AND DISEASES

The Seventh International Congress on Industrial Accidents and Diseases will be held at Brussels, Belgium, from July 22 to 27, 1935. The American committee of the congress is under the chairmanship of Dr. Fred H. Albee, New York, for the Section on Accidents, and that of Dr. Emery R. Hayhurst, Columbus, Ohio, for the Section on Industrial Diseases.

The American delegation to the congress will sail from New York on July 8 and will visit London, Amsterdam, The Hague and Paris and, optionally, Budapest. Physicians interested in the congress or in the medical tour in conjunction with it may address the secretary, Dr. Richard Kovacs, 1100 Park Ave, New York.

SOUTHEASTERN SURGICAL CONGRESS

The sixth annual assembly of the Southeastern Surgical Congress (comprising Alabama, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee and Virginia) will be held in Jacksonville, Fla., March 11 to 13. Desired information may be procured from Dr. B. T. Beasley, secretary-treasurer, 1019 Doctors Building, Atlanta, Ga.

Book Reviews

Physical Diagnosis. By Richard C. Cabot. Eleventh edition. Price, $5. Pp. 540, with 317 illustrations. Baltimore: William Wood & Company, 1934.

The life history of any popular medical book is always of interest. In 1900, Dr. Richard Cabot, then an assistant in clinical medicine at the Harvard University Medical School, took it on himself to write a book on the physical diagnosis of diseases of the chest. This book was intended for students; as Dr. Cabot stated, it contained nothing original but endeavored to describe in simple concise English how the chest should be examined and to do away with certain well worn myths regarding physical diagnosis that had been carried onward in nearly all textbooks. This volume was 310 pages long and contained among other novelties several roentgenograms of thoracic conditions bewilderingly difficult to appreciate and certainly impossible for the hard-headed clinician of those days to take seriously. However, the book was a distinct contribution to American medicine: It started teachers thinking how to improve clinical instruction.

The book was deservedly popular, and in 1901 and 1903 it was reprinted. In 1905, its title was changed to "Physical Diagnosis," and in order to cover this larger field it grew to be a volume 577 pages long. It was still crisply written and differed from other books of the same kind by virtue of its strength of personality. It made no attempt to describe technical processes with which Dr. Cabot was unfamiliar and gave no space to the description of tests which he believed to be useless. A review in the *Journal of the American Medical Association* (**45:**1185 [Oct. 14] 1905) stated: "The striking feature of Cabot's work is its individuality. The personality of the author is felt on every page. One is impressed with the fact that what is stated are the views of the author gained by personal experience and not those of someone else. . . . The strength of the book is in its honesty and in the courage of the writer and his shrewdness as a clinical observer and student. . . . Weight of authority does not prove to him the truth of a statement. He must prove it by his own experience; and if this is at variance with the authority, well and good; the result goes down in print just the same. Now, it is this critical spirit, this frank discussion of facts, this honest admission of his personal limitation, that livens the pages and makes one feel that one is having a heart-to-heart talk with the author. . . . For the practitioner, then, the book is highly entertaining and instructive, as well as for the student, if rightly used. It is full of valuable hints."

Nearly thirty years later the eleventh edition of "Physical Diagnosis" is fresh from the press. In form, it looks much like its progenitor, but has become a little better dressed and more costly. It is written in the same personal manner. Changes, of course, have crept in, for without doubt a certain amount of progress has been made with time in the art of physical diagnosis. This is shown especially in the chapters on diseases of the heart and lungs, where much greater stress is laid on the roentgen rays and the electrocardiograms as significant aids to inspection, percussion, palpation and auscultation. In the last edition, too, the author does not discuss laboratory procedures but limits himself more strictly to the proper interpretation of sign and symptoms.

The reviewer of the first edition pointed out the chief weakness of the book: It was incomplete in that such methods of physical examination as laryngoscopy, cystoscopy or ophthalmoscopy, with which Dr. Cabot was unfamiliar, were not described. The latest edition of the book makes no attempt to fill in these gaps. It remains, however, a sturdy example of usefulness. As it was in the beginning so it is now a highly entertaining and instructive book for the practitioner and student and full of valuable hints. May it continue to have a successful career!

Ergebnisse der Kreislaufforschung. Edited by Dr. B. Kisch. Volume IV. **Kreislaufstörungen und pathologische Histologie.** By Dr. Martin Nordman, Professor of General and Special Pathology at the University of Tübingen. Price, paper, 13.80 marks; cloth, 15 marks. Pp. 174, with 14 illustrations. Dresden: Theodore Steinkopff, 1933.

The treatment of the subject is from the point of view of histopathology. About ten pages are devoted to the history of the subject. After a brief review of the anatomy and physiology of the arteries, veins and lymph vessels, there is a brief discussion of the methods of investigation on living animals (capillary microscope, Sandison-Clark chamber and perfusion of organs). Then follows a detailed description of blood flow in the capillaries, smaller blood vessels and lymph vessels and the changes that these structures and the surrounding tissues undergo during normal variations, chemical stimulation, stasis, constriction and obstruction. Some space is devoted to general peripheral circulation at different levels of pressure and to the rôle played by the viscosity of the blood, the reticulo-endothelial system and the "filter-system" following the injection of dyes and serum. From this point on the author limits himself to the histopathology in man. Under each topic is a short preliminary description of the histology involved, followed by a detailed discussion of the topic. The material is divided into the following topics: (1) edema; (2) suppuration; (3) diapedesis; (4) necrosis; (5) growth of (*a*) simple granulation tissue, (*b*) nodule-forming granulation tissue (in response to tuberculosis, syphilis, typhus, rheumatic nodules and foreign bodies, etc.); (6) tissue repair, with a consideration of (*a*) atrophy, (*b*) scar formation, (*c*) chronic inflammation and (*d*) cirrhosis; (7) tumors (considered as an appendage); (8) cell and tissue metabolism under the headings fat, carbohydrate and protein, especially as it concerns the liver, thrombosis and amyloid and hyaline tissue. The last chapter is devoted to the pathology of the arteries, veins and lymph vessels. It considers arterial sclerosis, endarteritis obliterans, acute arteritis, aneurysms, hematomas, venous thrombosis, varicosities and elephantiasis. A few pages are devoted to angiospasm. The etiology of hypertension is discussed under neurogenic, hormonal and metabolic factors. The pathology of hypertension is considered from the point of view of observation of living tissue as well as from that of histologic specimens. Evidence is presented to show that the renal findings are the result, not the cause, of the hypertension. The vascular changes during local and general infections, disturbances of the thyroid and anemia are correlated with previous findings. Among his concluding remarks Nordman stresses the fact that the kind of stimulus is not as important as the strength of the stimulus in relation to the sensitivity of the body.

This monograph treats of the physiology more than the pathology of the vascular system. It is indexed and the bibliography, especially that of the European literature, is good. It summarizes satisfactorily the work of the last eighty years on the pathology of the vascular system.

The Distribution of the Currents of Action and of Injury Displayed by Heart Muscle and Other Excitable Tissues. By F. N. Wilson, A. G. MacLeod and P. S. Barker. Price, $1.50. Pp. 59. Ann Arbor, Mich.: University of Michigan Press, 1933.

This monograph is an important contribution to electrophysiology. The fundamental and comprehensive treatment of the distribution of electric currents resulting from the functional response of excitable tissues renders it of cardinal importance to all those dealing seriously with action potentials, whether in the field of electrocardiography or in other branches of physiology, namely, those dealing with the nervous and muscular systems and the electrical response of glands.

The authors analyze the problem of the flow of current in a homogeneous medium, with particular reference to currents of action and injury of the cardiac muscle. It is shown that the observed electrical phenomena can be simply explained on the hypothesis that the wave of excitation in the muscle is accompanied by an electrical source (positive) closely followed by a sink (negative) accompanying

the wave of excitation. A second sink followed by a source accompanies the wave of recovery, but inferences and experimental observations concerning it are developed in much less detail.

It is clearly pointed out that this interpretation is not only compatible with the Bernstein membrane hypothesis, but that it is a necessary consequence of it. In other words, the inferences as to source and sink imply nothing as to the detail of the mechanism or exact orientation of polarized membranes, etc., in the tissue. The electrical changes at a distant point are simply shown to correspond to what would occur if such sources and sinks were present, and reconciliation with the membrane hypothesis is complete.

Agreement with the experimental observations and most of the interpretations of Craib and disagreement with certain interpretations of Bishop and Gilson are expressed in a footnote. The exact basis for the criticisms of Bishop and Gilson is not explained in detail.

The monograph is useful as a simple exposition of the principles of the flow of current in volume conductors and should be helpful in the interpretation of the initial positive phase, sometimes called "positive artefact," preceding action potentials of nerve as well as muscle in situ.

The reviewing physiologists are grateful to the authors for relegating the mathematical derivations of the equations to an appendix, leaving in the text only those formulas which constitute the end-results of their efforts. The formulas are, happily, scattered through the text in such a way that the reader can hurdle them and read on without losing the thread of the argument.

Die akuten Zivilisationsseuchen; Ihre Epidemiologie und Bekämpfung. By B. DeRudden. Price, 16 marks. Pp. 286, with 49 illustrations. Leipzig: Georg Thieme, 1934.

As DeRudden points out in his general introduction, the term *Seuche* is to be given its usually accepted modern definition, viz., a disease which attacks a large number of persons in a locality and which besides possesses the quality of endangering life. Under this title he considers in a clear, brief but eminently practical manner the infectious diseases—measles, smallpox, whooping cough, scarlet fever, diphtheria and poliomyelitis.

The book is divided into two main parts, the first being devoted to the epidemiology and the second to the methods of suppression and eradication. There are, of course, numerous tabulations which constitute the statistical data.

Any innovation, if such may be claimed for the work, lies not so much in the presentation of new material as in the arrangement of the material. There is no classification of the subject matter into chapters, but each main division is subdivided into discussions which follow each other in logical sequence and for this reason stimulate interest and make reading easy.

Some interesting points in the epidemiology are the figures and the descriptions of classic instances of acute infections afflicting a susceptible population, as, for example, the epidemics of measles among the people of Iceland and poliomyelitis ravaging the relatively small population of an island in the Pacific ocean. The author draws from these examples and from others conclusions that are worthy of more than a passing thought.

The section devoted to prophylaxis contains material of interest to students of preventive medicine, and its chief importance lies in the description of the methods employed and the results obtained by sanitarians and health officers in Central Europe.

A large part of the book has been read by the reviewer with keen interest and pleasure, and the work may be warmly recommended to those who desire to obtain an up-to-date insight into the general status of infectious diseases in the world, but more especially in Europe.